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Highlights

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Poly(ADP-ribose) polymerases as modulators of mitochondrial activity

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- Activation of poly(ADP-ribose) polymerases-1 and -2 (PARP-1 and PARP-2) deteriorates mitochondrial activity.
- NAD^+ and ATP degradation are not coupled to each other upon PARP activation.
- PARPs interact with transcription factors modulating mitochondrial activity.
- PARPs can be positive regulators of mitochondrial output under sublethal stress.
- PARP inhibition is an attractive target for treating mitochondrial dysfunction.

Review

CellPress

Poly(ADP-ribose) polymerases as modulators of mitochondrial activity

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Mitochondria are essential in cellular stress responses. Mitochondrial output to environmental stress is a major factor in metabolic adaptation and is regulated by a complex network of energy and nutrient sensing proteins. Activation of poly(ADP-ribose) polymerases (PARPs) has been known to impair mitochondrial function; however, our view of PARP-mediated mitochondrial dysfunction and injury has only recently fundamentally evolved. In this review, we examine our current understanding of PARP-elicited mitochondrial damage, PARP-mediated signal transduction pathways, transcription factors that interact with PARPs and govern mitochondrial biogenesis, as well as mitochondrial diseases that are mediated by PARPs. With PARP activation emerging as a common underlying mechanism in numerous pathologies, a better understanding the role of various PARPs in mitochondrial regulation may help open new therapeutic avenues.

Poly(ADP-ribose) polymerases in the cellular regulation

The regulation of mitochondrial activity is critical in cell survival. Mitochondria are the major source of ATP as they house core metabolic pathways such as the Szent-györgyi-Krebs/tricarboxylic acid (TCA) cycle, oxidative phosphorylation, glutaminolysis, beta-oxidation, etc. Mitochondria are also essential in stress responses and they play an indispensable role in certain forms of cell death. A complex network of signal transduction pathways crosstalk and fine tune mitochondrial activity in cells, and the mitochondrial adaptation to stress. Reduced mitochondrial activity has been associated with several pathologies ranging from neurodegeneration to metabolic diseases [1].

PARPs (see Glossary) are predominantly nuclear enzymes that are involved in cellular stress responses, both as sensors of cellular damage, and as active participants in stress response (e.g., PARP-1 is a DNA damage sensor and a member of the DNA repair machinery) [2]. Although overactivation of some PARP family members (e.g., PARP-1 or PARP-2) was shown to hamper mitochondrial activity in response to oxidative stress and nutrient availability, the actual pathways through which PARPs regulate mitochondrial function are not fully understood. In this review, we will discuss the regulatory pathways that enable PARPs to impact on mitochondrial activity, highlight the novel roles of PARPs in mitochondrial dysfunction, the consequent pathological alterations, and the therapeutic potential of targeting these processes.

PARPs and PARylation

The PARP family of proteins consists of 17 PARPs in humans (PARP-1–17), and 16 PARPs (PARP-1–16) in mice [3]. PARPs are composed of functionally distinct domains, including – among others – a DNA-binding domain that enables PARPs to bind to RNA, damaged DNA, a catalytic domain, and different domains to support interaction with

Glossary

Basal and stimulated mitochondrial oxygen consumption: the measurement of oxygen consumption rates from isolated mitochondria, or from intact cells or organs *in vitro* helps to evaluate mitochondrial (dys)function and disease, because ADP-dependent oxygen consumption directly reflects coupled respiration or oxidative phosphorylation.
Macrodomain: macrodomains (also known as A1pp domains) are domains capable of binding ADPR and other NAD^+ metabolites. Proteins containing macrodomain(s) can remove ADPR from proteins.
poly(ADP-ribose) (PAR): the end product of the poly(ADP-ribosyl)ation reaction. NAD^+ is cleaved to ADP-ribose (ADPR) and nicotinamide, and then ADPR moieties are joined to each other making large, branched polymers.
poly(ADP-ribose) glycohydrolase (PARG): a main PAR degrading enzyme. PARG is a multidomain protein that has numerous splice variants that can be found in most cellular compartments, such as the mitochondria.
poly(ADP-ribose) polymerases (PARPs): also called diphtheria toxin-type ADP-ribose transferases (ARTDs), are a family of enzymes sharing a common catalytic domain. PARPs become activated by DNA breaks or by signaling pathways. Activated PARPs cleave NAD^+ into nicotinamide and ADP-ribose and covalently attaches a PAR polymer to itself and other suitable acceptors. Via PARylation or protein–protein interactions PARP regulates chromatin organization, DNA repair, transcription and replication. Excessive DNA damage can also trigger a PARP-mediated necrotic cell death pathway. Not all PARPs are capable of forming PAR polymers and some catalyze the addition of a single or a few ADPR units to target proteins (mono and oligo ADP-ribosylation, respectively) or are inactive.
Parthanatos: a special form of cell death that is distinct from apoptosis or necrosis. It is referred to as PARP1-dependent cell death as it is characterized by PARP activation, PARylation, mitochondrial transition, AIF translocation, and DNA fragmentation, but lack caspase activation.
PARylation: is a post-translational protein modification performed by PARP enzymes. It involves the cleavage of NAD^+ into ADP-ribose (ADPR) and nicotinamide (NAM). ADPR is then bound to the side chains of glutamate, aspartate or lysine amino acids of proteins. Then ADPR moieties are joined to form PAR that is a large, branched polymer ranging up to 200 ADP-ribose units.

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proteins or NAD^+ metabolites (for detailed overviews see [2,4,5]). PARPs are involved in DNA repair processes, transcriptional regulation, cell death in oxidative stress related pathologies, and metabolic and immune regulation [6].

PARylation is an evolutionarily conserved post-translational modification reaction whereby activated PARP cleaves NAD^+ into nicotinamide and ADP-ribose and covalently attaches an ADP-ribose polymer (ADPR) to itself and other acceptors, such as histones or other DNA-associated proteins. Because PAR polymers have negative charge, they may change the conformation of acceptor proteins or disrupt protein–protein and protein–nucleic acid interactions. PAR can also act as an interaction surface for certain DNA repair proteins [7]. PARP-1 and PARP-2 can inhibit themselves through self-PARylation (autoPARylation), and can modulate the biochemical activity of a plethora of proteins through trans-PARylation. Despite sequence similarity in the catalytic domains between PAPR family members, only PARP-1, PARP-2, and tankyrases are known to produce long PAR polymers, while other PARP enzymes are defective in elongation or are inactive [3]. Hence, the majority of both basal and stimulated cellular PARP activity is attributed to PARP-1 (85–90%) and PARP-2 (10–15%) [2]. Activation of the nuclear PARP-1, -2, and -3 can be triggered by single or double strand breaks in DNA, frequently induced by oxygen or nitrogen reactive species (ROS, RNS), or abnormal DNA structures [2]. There is accumulating evidence that alternative pathways of PARP-1/2 activation exist, such as increases in intracellular calcium, kinase cascades (e.g., ERKs), mono-ADP-ribosylation, and acetylation, whereas self-PARylation, phosphorylation by protein kinase C (PKC), or SUMOylation are inhibitory [2,6,8].

The PAR polymer has short half-life and it is rapidly degraded to ADPR. The enzymology of PAR degradation is complex, as several enzymes are capable of degrading PAR. Poly(ADP-ribose) glycohydrolase (PARG) is an efficient PAR degrading enzyme that can cleave the ends of the PAR polymer or within the chain. Several PARG isoforms exist, due to alternative splicing, that can be found in most cellular compartments [9]. Besides PARG, ADP-ribosylacceptor hydrolase 3 (ARH3), ADP-ribosyl lyase and macrodomain-containing proteins are also important regulators of cellular PAR levels [2,5,9–11]. ADPR can be further metabolized to AMP by nucleoside diphosphate linked to X (NUDIX) pyrophosphatases [12].

PARP-mediated damage of mitochondrial function

PARP activation (that is mostly attributed to the activation of PARP-1) promotes a rapid loss of mitochondrial potential and decreases basal and stimulated mitochondrial oxygen consumption [13]. PARP-1 activation reduces the activity of mitochondrial complex I [14], NADH-oxidase, and NADH Q1-reductase [15], resulting in electron transport chain uncoupling and superoxide production [16]. Mitochondrial architecture is distorted and is characterized by swelling and the disorganization of the trabecular system of the inner mitochondrial membrane [16]. Subsequently, mitochondrial transition pores (MTPs) open releasing mitochondrial content such as cardiolipin, apoptosis inducing factor (AIF), cytochrome c or caspases [16–18]. Furthermore, PARP-1 activation impairs mitophagy [19], which is a process through which damaged portions of the mitochondria can be removed.

PARP activation is energetically catastrophic to the cell, as it is accompanied by reductions in cellular NAD^+ and ATP levels, thus leading to mitochondrial energy failure. Originally, reductions in ATP levels were linked to the attempt of the cell to resynthesize NAD^+ through nicotinamide mononucleotide adenylyltransferase (NMNAT) and phosphoribosyl pyrophosphate synthetase (PPS), an energetically demanding reaction [18]. However, other pathways that may cause more profound reductions in ATP, independent of NMNAT and PPS, have been identified.

Results from Chiarugi *et al.* [20] suggest that ATP loss is not a direct result of the attempt of the cell to resynthesize NAD^+. ADPR, the end product of PAR hydrolysis, can be converted into AMP by NUDIX pyrophosphatases [12]. Increases in AMP levels upon PAR hydrolysis block mitochondrial adenine nucleotide translocator (ANT), hampering mitochondrial ADP uptake and ATP release [12], and slowing down ATP release from mitochondria. In addition, the bypass to recharge ATP from ADP (2 ADP $\rightarrow$ AMP + ATP), through adenylate kinase, is limited, due to the low ADP availability under conditions of PARP-1 overactivation [21].

PAR or PARylated PARP-1 can escape the nucleus and damage mitochondrial function. A recent study demonstrated that ring finger protein 146 (RNF146, Iduna), a cytoplasmic E3-ubiquitin ligase and PAR polymer-binding protein, interacts with PARP-1 and protects against PAR polymer-induced mitochondrial dysfunction and cell death. Therefore, PAR binding to mitochondria can be prevented by Iduna [22], suggesting that Iduna can sequester PAR to the cytosol and hence protect against PAR-induced mitochondrial collapse. Furthermore, Iduna can direct cytoplasmic PARylated PARP-1 (and likely other PARylated proteins) to the proteasome for degradation [23].

An acceptor of PAR on the mitochondrial surface is hexokinase (HK) [24,25]. HK binds to the mitochondrial surface, where it interacts with voltage-dependent anion channels and regulates ADP/ATP exchange between the cytosol and mitochondria. Mitochondrial ADP import is vital for mitochondrial ATP synthesis and for maintaining the rate of mitochondrial oxidation, while ATP regulates glycolytic flux through glucose phosphorylation [26]. Therefore, HK regulates the coupling between glycolysis and mitochondrial oxidation, and the release of HK from the mitochondrial surface induces mitochondrial dysfunction and cell death [26]. In addition to these findings, PAR binding to apoptosis inducing factor (AIF), a cell death-inducing mitochondrial protein, is required for AIF release from mitochondria [27].

PARP activity may exist in the mitochondrial matrix. There is consensus in the literature that mitochondria possess glycohydrolase activity (the activity necessary for PAR degradation) with ARH3 being the major component [28]. Although the existence of mitochondrial PARP activity is debated, there are data that show the presence of PARylated proteins in isolated rat liver mitochondria [29,30], mitochondrial PARP activity [29,31], or identify

mitochondrial malate dehydrogenase as a PARP-1 interacting protein [32]. However, these studies were based on the extraction of PARylated proteins using a PAR antibody and given the existing discrepancies between proteins identified by the different studies [29,30]; additional, non-immunological methods are required to verify these findings. Importantly, when PARP-1 was overexpressed in mitochondria, *in vitro*, mitochondrial PARylation increased, which was accompanied by decreased mitochondrial output and unaltered glycolytic flux [33], highlighting a possible functional consequence of mitochondrial PARylation. Taken together, PAR-degrading activity appears to be present in mitochondria, while well-defined PARP activity or presence is missing. However, it seems that the PARylation of mitochondrial proteins may profoundly reduce mitochondrial oxidative phosphorylation and probably influence mitochondrial NAD^+ levels and hence the activity of NAD^+-dependent enzymes in the mitochondria.

Interference of PARPs with signal transduction pathways

Signal transduction pathways integrate environmental signals into mitochondrial regulation. The phosphatidylinositol3-kinase (PI3K)–Akt–glycogen synthase kinase-3 (GSK3) and AMP activated kinase (AMPK) pathways were shown to be modulated by PARP [34]. The phosphorylation and activation of Akt stabilizes mitochondrial function under stress conditions by preventing mitochondrial permeability transition (MPT). PARP inhibition by structurally different PARP inhibitors increases the activity of PI3K [35] and Akt [34-36] thus preventing the loss of the mitochondrial membrane potential upon oxidative damage [34]. Tankyrases are also likely to possess regulatory properties over mitochondria by interacting with GSK3 [37].

AMPK is a major cellular energy sensor. It detects and reacts to fluctuations in the AMP:ATP ratio, and is activated in response to low cellular energy charge. AMPK activation induces transcriptional programs that enhance oxidative metabolism to recharge cellular energy stores [38]. PARP-1 activation results in increased AMPK activity [39–41] that might be linked with the degradation of PAR to AMP by NUDIX pyrophosphatases and the change in the AMP:ATP ratio [12]. AMPK can physically interact with and activate PARP-1 through phosphorylation on Ser^{177} [42,43], completing a feedforward loop between PARP-1 and AMPK. Interestingly, the deletion of PARP-1 does not affect AMPK activity [44]. The crossactivation between AMPK and PARP can be an important survival pathway in cells undergoing stress, not only through inducing mitochondrial activity, but also by facilitating autophagy [39,40].

As mentioned earlier, PARP activation induces mitochondrial uncoupling and reactive oxygen species production [16]. This observation suggests that PARP activation can alter mitochondrial ROS signaling; however, that possibility had not been studied.

Mitochondrial regulation through modulating transcription

Interaction between sirtuins and PARPs

Sirtuins are a family of seven (SIRT1–7) NAD^+-dependent protein deacetylases in humans [45]. As a consequence, enhanced NAD^+ synthesis, decreased NAD^+ breakdown or cellular energy stress that manifests as decreases in the cellular NAD^+/NADH ratio can activate sirtuins [2,45]. The activities of the nuclear SIRT1 and the mitochondrial SIRT3 were shown to be modulated by PARPs. Activation of SIRT1 and SIRT3 cooperatively enhances mitochondrial activity through deacetylating several target proteins. SIRT1 deacetylates and activates the transcription cofactor FOXO1, the coactivator peroxisome proliferator activated receptor cofactor-1α (PGC-1α), or p53 [45], and triggers transcriptional programs that induce mitochondrial biogenesis. SIRT3 deacetylates several proteins in mitochondrial complexes I–V boosting mitochondrial activity [45]. SIRT1 activation is associated with improved performance of mitophagy, mitochondrial unfolded protein response (mtUPR), and the maintenance of mitonuclear protein balance [46].

SIRT1 and PARP-1 mutually inhibit each other's activity. They are both nuclear enzymes sharing the same substrate, NAD^+; however, PARP-1 has higher affinity for NAD^+, ($K_m \sim$ 20–60 μM) than SIRT1 ($K_m \sim$ 100–300 μM) [2]. In addition, PARP-1 is more effective in NAD^+ breakdown than SIRT1, as PARP-1 has higher K_m/K_{cat} value ($K_m/K_{catPARP\text{-}1}$ = 6000 $s^{-1}M^{-1}$) than SIRT1 ($K_m/K_{catSIRT\text{-}1}$ = 350 $s^{-1}M^{-1}$) [2]. Due to its higher affinity to NAD^+ and quicker turnover rate, activated PARP-1 can limit NAD^+ availability for SIRT1 [2]. Hence, pharmacological inhibition or genetic deletion of PARP-1 boosts nuclear NAD^+ levels [44,47,48]. In skeletal muscle and brown adipose tissue, increases in NAD^+ levels are translated into higher SIRT1 activity and improved mitochondrial output, mitonuclear protein balance, and better performance of the mtUPR [48].

Its lower affinity to NAD^+ and slower catalytic turnover rate of SIRT1, makes it unlikely that SIRT1 could efficiently limit NAD^+ to inhibit PARP-1 [2]. However, PARP-1 is active as an acetylated protein and SIRT1 is capable of deacetylating, and hence inhibiting, PARP-1 activity [8]. SIRT1 activation, the concomitant inhibition of PARP-1 and the enhancement in mitochondrial biogenesis had been demonstrated to protect cells from PARP-mediated oxidative damage [8,49].

Recently, a link between mitochondrial SIRT3 expression and PARP-1 activation was established. In neurons, N-methyl-D-aspartate (NMDA)-induced excitatory cell injury activated PARP-1, and this was followed by a sustained enhancement of SIRT3 mRNA and protein expression [50]. Enhanced production of reactive oxygen/nitrogen species and modulation of NAD^+ levels were suggested to be involved in the upregulation of SIRT3 expression [50], which in turn positively impacted cell survival after NMDA injury.

PARP-2 also influences SIRT1 activity. Depletion of PARP-2 resulted in enhanced SIRT1 activity and increased mitochondrial biogenesis in several *in vitro* model systems [51–54]. Silencing of PARP-2 in these studies resulted in increased SIRT1 mRNA and protein expression and enhanced SIRT1 activity, independent of changes in NAD^+ levels. Consequently, it was shown that PARP-2 acts as a suppressor of SIRT1 promoter activity [51–53]. Another recent study [51] identified *miRNA149* as an upstream repressor of PARP-2 expression that consequently induced

SIRT1 expression in response to fasting. Thus, changes in PARP-2 expression were shown to integrate metabolic signals (such as fasting or high fat feeding) or cellular redox status (such as oxidative stress) into changes in SIRT1 expression and activity in skeletal muscle, liver, and the vasculature, fine tuning mitochondrial output [51–53]. Interestingly, PARP-1 does not modulate the activity of the SIRT1 promoter [44]. These findings highlight key differences in the mode of action of PARP-1 and PARP-2.

The induction of PARP-7 was shown to bring about major metabolic changes in the liver characterized by decreases in NAD^+, and suppressed expression but enhanced acetylation of PGC-1α [55]. Such biochemical changes are the hallmarks of SIRT1 inhibition; however, whether these changes translate into suppressed mitochondrial activity has not been investigated. An overview of the PARP-mediated pathways regulating mitochondrial activity is shown in Figure 1.

Interactions with nuclear respiratory factors (NRFs)

NRF-1 and NRF-2 are nuclear transcription factors that, upon activation, induce the expression of key mitochondrial genes, such as cytochrome c and mitochondrial transcription factor A, leading to enhanced mitochondrial activity [56]. NRFs bind to well-defined, guanine/cytosine (GC)-rich consensus DNA sequences, also called antioxidant response elements (AREs), and interact with cofactors, such as PGC-1α and PGC-1β to efficiently activate

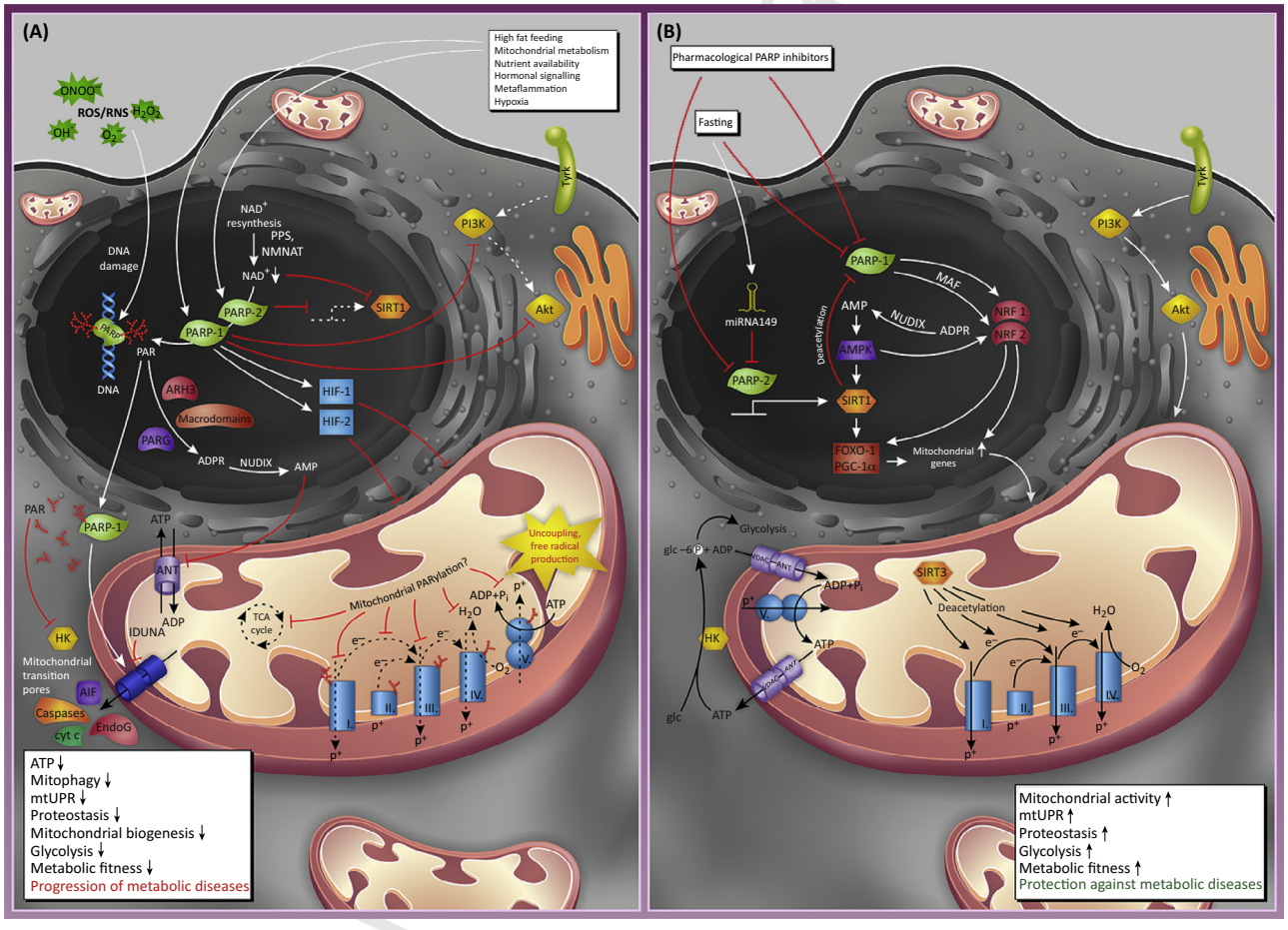

Figure 1. Overview of the poly(ADP-ribose) polymerase (PARP)-mediated pathways regulating mitochondrial activity. Upon acute, uncontrolled PARP activation **(A)** PARP-1 and PARP-2 bind to DNA and at the expense of NAD^+, synthesize PAR, leading to marked reductions in cellular NAD^+ and ATP. In this context, ATP loss stems from elevations in AMP due to PAR degradation and concomitant inhibition of ANT. The sirtuin SIRT1 is inhibited by NAD^+ loss, the acetylation of the coactivator peroxisome proliferator activated receptor cofactor-1α (PGC-1α) and the transcription co-factor FOXO1 increases, leading to lower expression of genes involved in mitochondrial biogenesis. Hypoxia-inducible factor (HIF)-1 and HIF-2 can be activated, which suppresses mitochondrial activity. PAR is exported from the nucleus and suppresses glycolysis and mitochondrial activity. The complexes of the electron transport chain can be inhibited by mitochondrial PARylation, which reduces mitochondrial membrane potential, and enhances superoxide production and the opening of the mitochondrial transition pores (MTPs). PARP activation reduces mitochondrial output and the ability of mitochondria to self-repair (reduced mitophagy and mitonuclear protein imbalance), a dysfunction underlying several metabolic disorders.
In recovery from sub-lethal damage **(B)** the activation of several pathways culminate in sustained mitochondrial activity and cell survival. SIRT1 activation inhibits PARP-1 through deacetylation. PARP-2 expression is suppressed by *miRNA149*, which enhances SIRT1 expression. High AMP levels induce AMP activated kinase (AMPK), which supports SIRT1 activity and the activity of nuclear respiratory factors (NRFs). SIRT1 and NRFs activate PGC-1α and FOXO1, inducing transcriptional programs that boost mitochondrial biogenesis. Enhanced expression of SIRT3 leads to deacetylation and activation of the electron transport chain complexes. These effects culminate in the stabilization or enhancement of mitochondrial activity, and stabilization of mitochondrial self-repair (mitophagy and mitochondrial proteostasis). PARP inhibition, and thus stabilization or enhancement of mitochondrial activity, can improve metabolic pathologies or metabolic parameters.
Abbreviations: Akt, protein kinase B; ANT, adenine nucleotide translocator; ARH3, ADP-ribosyl-acceptor hydrolase 3; cyt c, cytochrome c; Endo G, endonuclease G; HK, hexokinase; mtUPR, mitochondrial unfolded protein response; PARG, poly(ADP-ribose) glycohydrolase; PI3K, phosphatidylinositol 3-kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; TyrK, tyrosine kinase receptor; VDAC, voltage-dependent anion channel.

mitochondrial genes [56]. NRF activity can be triggered by ROS/RNS, Akt, or AMPK [56].

NRF-1, in complex with DNA-dependent protein kinase (DNA-PK), Ku80, Ku70, and topoisomerase Iiβ, was shown to bind to PARP-1 [57]. PARP-1 binds to and PARylates the DNA binding domain of NRF1, however PARylated NRF-1 does not lose its affinity to PARP-1 [57]. The NRF-1/PARP-1 complex binds to the human cytochrome c promoter and facilitates cytochrome c expression [57]. Furthermore, PARP-1 was also shown to act as a transcriptional coactivator for NRF-2. PARP-1 binds NRF2 indirectly through the adaptor protein Maf and upregulates the its transcriptional activity [58]. It is important to note that the interactions between PARP-1 and NRF-1/2 are independent of the enzymatic activation of PARP-1, which can be crucial in cells recovering from sublethal oxidative injury (Box 1).

Interaction with hypoxia-inducible factors (HIF)

HIF-1 and HIF-2 are transcription factors with an indispensable role in the accommodation of hypoxia. HIFs facilitate the adaptation to hypoxia through initiating transcriptional programs that induce metabolic pathways not requiring oxygen (e.g., glycolysis), while repressing the oxygen dependent mitochondrial oxidation [59].

Martin-Oliva *et al.* [60] were the first to show that HIF-1-induced suppression of Complex II and Complex IV in deferoxamine-induced hypoxia depends on PARP-1 activation and the PARP-1-mediated production of ROS [61–63]. The inhibition of PARP-1 blocks HIF-1 activation and expression of HIF-dependent genes, among them the factor inhibiting HIF (FIH) [64,65]. Blunted induction of HIF-1 and FIH expression changes the dynamics of HIF-1 activation: in cells undergoing PARP inhibition despite low HIF-1 activity, HIF-1 activity is maintained longer after release from hypoxia due to the lower levels of FIH [64]. PARP-1 also forms a physical complex with HIF-2 and promotes the expression of HIF-2 mediated genes [66]. Thus, PARP-1 activation facilitates HIF-1 and HIF-2 activation contributing to down-regulation of mitochondrial activity. Importantly, HIF-1 and HIF-2 can also facilitate neoplastic transformation [59].

Other transcription factors with possible mitochondrial regulatory role

As mentioned earlier, PARP-1 has widespread transcriptional effects [67] and influences the activity of several proteins, including p53. The protein p53 was shown to be PARylated in an animal model of Parkinsonism [68], a disease with known metabolic alterations, suggesting that mitochondrial activity could be modulated through p53 PARylation. PARP-modulated metabotropic transcription factors are summarized in Table 1.

Box 1. PARP–nuclear receptor interactions

Nuclear receptors (NRs) are ligand activated transcription factors that play key roles in multiple cellular functions including cell differentiation and proliferation, and in metabolic homeostasis. NRs translate metabolic demands into transcriptional programs facilitating metabolic adaptation [86]. PARPs interact with numerous NRs [72] suggesting that PARPs may impact on mitochondrial activity through modifying NR activity, which remains to be explored in future studies

PARP-1 and PARP-2 mediate the activity of numerous NRs. PARP-1 may act as coregulator for estrogen receptors (ERs), progesterone receptor (PR), retinoic acid receptor (RAR), thyroid hormone receptor (TR), retinoid X receptor (RXR), peroxisome proliferator activated receptor (PPARs), neuron-derived orphan receptor-1 (NOR-1) [72], and PARP-2 for ERα and PPARs [87]. PARP-1 can act as either a corepressor or coactivator of NRs depending on the cell type, tissue or type of treatment. Interaction surfaces on PARP-1 had been mapped to the second zinc finger and to the BRCT domain, while in PARP-2 such studies were not conducted. PARP-1 can act through various modalities such as PARylating histones to make chromatin more accessible, PARylating transcription factors to modulate their activity, direct protein–protein or DNA–protein interactions. It seems that PARP-2 is a constitutive cofactor of the PPARs [87], while it is under debate whether the activity of PARP-2 is necessary for transcriptional regulation. Interactions between PARPs and NRs have major impact on metabolism, gene expression and cell survival.

PARP-mediated diseases associated with mitochondrial dysfunction

Diseases associated with acute mitochondrial damage

Under pathological conditions associated with mitochondrial dysfunction, the induction of mitochondrial biogenesis alleviates disease burden. Restoring mitochondrial biogenesis not only restores mitochondrial energy production and stabilizes the coupling of the mitochondrial electron transport chain, but revitalizes the flux of mitochondrial biosynthetic pathways. As we discussed earlier, PARP activation deteriorates mitochondrial function, and consequently, several mitochondrial pathologies are associated with or are triggered by PARP activation. PARP inhibition, or the genetic deletion of *PARP-1* or *PARP-2* mitigates damages to mitochondrial activity, and therefore protects against these diseases.

PARP activation triggered by extensive oxidative DNA injury, and the consequent mitochondrial dysfunction and cell death, has been implicated in numerous pathological processes (e.g., ischemia–reperfusion injury, inflammatory diseases, burn, Parkinsonism, Alzheimer's and Huntington's diseases, and multiple sclerosis toxicity of cytostatic drugs, among others) [18,69,70]. PARP activation, and the consequent mitochondrial transition, governs the choice of cells between types of cell death [18]. Upon extensive PARP activation, mitochondrial activity is impaired and ATP levels drop, pushing cells into necrosis [18]. A limited set of cell types, such as neurons, can undergo parthanatos, a specialized type of cell death characterized by PARP activation, mitochondrial transition, AIF translocation, DNA fragmentation, and the lack of caspase activation [27]. PARP inhibition conserves mitochondrial activity and cellular ATP; therefore, cells either can repair their DNA or can undergo the ATP-dependent apoptotic program that is characterized by lower inflammation and better outcomes, as compared to necrosis [18]. It is important to note that PARP activation-elicited cell death can also be physiological, for example, in osteoblasts during osteogenic differentiation [71].

PARPs, mitochondria, and metabolic diseases

PARP activation has equal importance in those pathologies that are characterized by long-term mitochondrial dysfunction, rather than cell death. It is very likely that

Table 1. PARP-interacting metabotropic transcription factors modulating mitochondrial activity

Transcription factor	PARP partner	Experimental modulation of PARP expression or PARP activity[a]	Effect on mitochondria	Refs
FOXO1	PARP-1 PARP-2	*PARP-1* shRNA, PJ34 *PARP-2* shRNA	PARP-1 regulates FOXO1 through mediating SIRT1 activity. Active SIRT1 deacetylates and activates FOXO1, inducing mitochondrial activity. Silencing of PARP-2 induces mitochondrial activity through inducing SIRT1 expression that deacetylates FOXO1.	[44,52]
HIF-1	PARP-1	*PARP-1* knockout, DPQ, PJ34	PARP-1 inhibition prevents the HIF-mediated suppression of Complex II and Complex IV activity.	[60–65]
HIF-2	PARP-1	*PARP*-1 knockout, PJ34	Unknown	[66]
NRF-1	PARP-1	Overexpression of deletion mutants of *PARP-1, PARP-1* shRNA	NRF-1 and PARP-1 jointly regulate the expression of cytochrome c.	[56,57]
NRF-2	PARP-1	*PARP-1* overexpression, *PARP-1* knockout	PARP-1 overexpression enhances NRF-2 binding to NRF-2 specific promoters.	[58]
SIRT1	PARP-1 PARP-2 PARP-7	*PARP-1* shRNA, PJ34, TIQ, Iniparib, Olaparib, ABT-888, MK4827 *PARP-2* shRNA PARP-7 overexpression	PARP-1 and SIRT1 activity are inversely coupled. PARP-1 activation depresses, while PARP-1 inhibition/silencing induces mitochondrial activity. Silencing of PARP-2 induces mitochondrial activity through inducing SIRT1 expression. PARP-7 activation may inhibit SIRT1.	[8,19,44,47–49, 51–55,83]
SIRT3	PARP-1	PJ34, DPQ	PARP inhibition by DPQ suppresses NMDA-induced accumulation of SIRT3 in the mitochondria.	[50]
PGC-1α	PARP-1 PARP-2	*PARP-1* shRNA, PJ34 *PARP-2* shRNA	PARP-1 regulates PGC-1α through mediating SIRT1 activity. Active SIRT1 deacetylates and activates PGC-1α. Silencing of PARP-2 induces mitochondrial activity through inducing SIRT1 expression that deacetylates PGC-1α.	[8,19,44,47–49, 51–54,83]

[a]Abbreviations: DPQ, PJ34, PARP-1 inhibitors; shRNA, small hairpin RNA; TIQ, PARP-1 inhibitor.

the dysfunction of the PARP-mediated regulatory pathways (e.g., the balance of the SIRT1/PARP-1 interaction, or of HIF activation) is a major pathogenic factor in complex diseases, such as metabolic disorders, cancer, aging, lifespan, and healthspan regulation.

The role of PARPs in metabolism is complex. Global deletion of PARP-1 in mice enhances food uptake and alters feeding behavior [44,72], suggesting alterations in metabolic sensing and/or in the central nervous system. Regulation of appetite and circadian phase entrainment relies on changes in mitochondrial activity in the nuclei of the hypothalamus [73]; therefore, it is very likely that PARP-1 controls appetite and circadian rhythm through modulating mitochondrial output. In support of this hypothesis, the hepatic circadian phase entrainment is regulated by the interplay of PARP-1 and SIRT1 [74].

The deletion or pharmacological inhibition of PARP-1 and PARP-2 leads to a catabolic shift in metabolism through inducing SIRT1 activity in skeletal muscle, liver, and brown adipose tissue, which translates into enhanced mitochondrial biogenesis [72]. Higher levels of mitochondrial activity consequently lead to lower adiposity and lower body mass [44,48,52]. *PARP-1* and *PARP-2* knockout mice exhibit skeletal muscle enriched in mitochondria rich type I fibers that improves insulin sensitivity [72]. *PARP-1* deletion in mice or pharmacological PARP inhibition improves glucose tolerance [44,48], the consequence of enhanced mitochondrial activity.

These metabolic changes confer protection against numerous metabolic diseases, such as obesity and insulin resistance [44,48,52], the hallmarks of the metabolic syndrome. Metabolic syndrome can progress into type 2 diabetes (T2D) when hyperglycemia develops. The features of T2D are ameliorated upon the deletion of *PARP-1* or pharmacological PARP inhibition [44,48]. Beta cell death in type I diabetes (T1D) or in advanced T2D is a PARP-mediated process involving mitochondrial transition, an event that is blocked by the deletion of *PARP-1* [18,72].

The sequel of the metabolic syndrome and T1D or T2D has PARP activation associated features. These diseases encompass diabetic complications such as cardiovascular diseases or atherosclerosis [18,72], which also involves PARP activation [75,76]. However, these are complex diseases and pathogenesis is not limited to simple changes in metabolism but involve other components, including inflammation. PARP-1 and PARP-2 activation may also promote proinflammatory processes via multiple mechanisms. These involve the activation of proinflammatory transcription factors that induce the transcription of chemokines and cytokines [e.g., tumor necrosis factor α (TNFα), interleukin-1β (IL-1β)], intercellular, vascular, and liver adhesion molecules (I-CAM, V-CAM, L-CAM),

inducible nitric oxide synthase or cyclooxygenase-2 that enhance the homing, extravasation, and activation of inflammatory cells [77]. Logically, PARP inhibitors exert anti-inflammatory properties. Although the role of PARPs in metabolic inflammation (also termed metaflammation) has not been explored, it is likely that limiting metaflammation by PARP inhibition could be an important target in combating metabolic diseases and their complications.

The possible role of PARPs in cancer cell metabolism

Cancer cells are characterized by an uncoupling of glycolysis from mitochondrial anabolic processes (TCA cycle and terminal oxidation) leading to decreased mitochondrial oxidation and enhanced glycolytic flux, even in the presence of oxygen, a phenotype called the Warburg effect [78]. Warburg-type metabolism supports the high cell division rate in tumors, while reverting Warburg-type metabolism slows down proliferation [78]. Several metabolic enzymes are now classified as Warburg enzymes, as changes in their expression or mutations were associated with tumors in humans or in animal models [78]. Recent data provided evidence that Warburg enzymes can be involved in cell division, cell death, and energy sensing [79].

Highly selective PARP inhibitors are in clinical trials to combat neoplasms through impairing DNA repair processes in these cells [80]; however, a large body of evidence suggests that PARP inhibitors can have anti-Warburg properties as well [81]. PARP activation suppresses the mitochondrial oxidation [16] that is common with Warburg-type metabolism, while PARP inhibition induces mitochondrial activity [44,48], which is an anti-Warburg feature. Along the same lines, HK is crucial for coupling glycolysis and mitochondrial oxidation [26]. HK dissociates from the mitochondrial surface upon Iduna-mediated PAR efflux from the nucleus [23–25], suggesting that PARP activation can in fact uncouple glycolysis and mitochondrial anabolism. Furthermore, HIF activation, that suppresses mitochondria and induces glycolysis (Warburg-type metabolism) and neoplastic transformation, is supported by PARP activation [60–62,64,66]. The interaction between the PI3K pathway and PARPs can be implicated in Warburg-type metabolic rearrangements, as PARP inhibitors and PI3K pathway inhibitors can potentiate each other's antitumor activities [75,82]. Furthermore, it is conceivable that tankyrases or PARP-10 may also have anti-Warburg properties through inducing mitochondrial activity, since these enzymes interact with GSK3 or *c-myc* [5,37]. The contribution of the anti-Warburg effect of PARP inhibition in cancer treatment is an open question to be investigated.

PARP inhibition, a double-edged sword in mediating healthspan and lifespan

Work from the laboratory of Alexander Bürkle showed in the late 1990s that PARP activity in the lymphoblastoid cells of centenarians is higher than in those of controls (20–70 years of age) [76]. Subsequent studies have unveiled a similar relationship between PARP activity and lifespan, suggesting that increases in PARP activity promote longevity through facilitating the recognition of DNA damage and the repair of the damaged sites [76] – a long-standing cornerstone finding of the PARP field. However, a recent study in which an extra copy of PARP-1 was introduced into mice [76] revealed that the PARP-1 transgenic mice indeed had a lower incidence of certain malignancies; however, they developed age-related diseases that were linked to mitochondrial dysfunction (e.g., obesity or impaired glucose metabolism) or inflammation [76]. These data are in clear agreement with findings showing that PARP activation impairs [16] mitochondrial biogenesis and mitochondrial activity, which seems to be the underlying cause of the higher incidence of the metabolic diseases in PARP-1 transgenic mice. On the other hand, enzymatic inhibition or genetic deletion of PARP-1 impairs DNA repair processes and induces genomic instability, but improves mitochondrial biogenesis and mitochondrial activity, which confers protection against metabolic diseases [44,47,48,83]. As an example, chronic inhibition of PARP in aging rats improves cardiovascular function and energetics [84]. Available data strongly suggest that the distortion of the balance between PARP and SIRT1 activity is an important factor in aging-related mitochondrial dysfunction and aging-related metabolic diseases (for review see [2]).

Concluding remarks and future perspectives

PARPs are members of a large, evolutionarily conserved, protein network. PARPs integrate metabolic signals [44], DNA damage [53], oxidative stress [16], and stress to mitochondrial and other metabolic processes. PARP activation induces several pathways that hamper mitochondrial activity (inhibition of SIRTs, activation of HIFs, NAD^+ and ATP depletion, or mitochondrial PARylation). Depending on the extent of PARP activation, the induction of these pathways may culminate into cell death or mitochondrial dysfunction, contributing to the pathology of numerous diseases affecting humans. The palette of the diseases that involve PARP activation and mitochondrial dysfunction has expanded recently by the inclusion of metabolic and liver diseases, aging, and cancer [72,85]. Predictably, this list will further grow with the addition of other inflammatory diseases.

A major leap forward in the field was the identification of PARP-mediated positive regulators of mitochondria (AMPK, SIRT1, and SIRT3). Some of these pathways are independent of PARylation (e.g., NRFs [57,58]), and are hence capable of preserving mitochondrial activity under stress conditions. These feedforward pathways might be important for cells to recover from sublethal PARP-mediated stress situations [42,49,50]. In other words, while extensive PARP activation triggers cell death due to energy failure, mild PARP-1 activation may support mitochondrial recovery on a longer timeline. PARP-mediated mitotropic pathways act in a concerted fashion; however, as of today, an integrative approach to study these processes involving metabolomics, proteomics, and the use of new generation of highly selective PARP inhibitors is missing. There are also numerous open questions in the field to be addressed (Box 2).

Nevertheless, the negative impact of PARP activation on mitochondrial function appears to be a common central underlying mechanism in PARP-mediated processes and

Box 2. Outstanding questions

- Do other members of the PARP family influence mitochondrial activity?
- Are there yet undiscovered PARP-mediated pathologies on which mitochondrial dysfunction has major impact?
- Do PARPs modulate the activity of other mitochondrial sirtuins?
- Which are the major pathways that reduce cellular ATP upon PARP activation? Are those activated in a cell or tissue-specific manner?
- What is the role of the nuclear, cytoplasmic and mitochondrial NAD^+ pools upon PARP activation and in the recovery following PARP activation?
- How does the genetic background affect PARP activation and other biological functions of PARPs?

diseases. These diseases affect a large population, putting heavy burden on patients and societies. Therefore, a better understanding of the networks connecting PARPs and mitochondria has clear therapeutic relevance and warrants further investigation.

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References

1 Nunnari, J. and Suomalainen, A. (2012) Mitochondria: in sickness and in health. *Cell* 148, 1145–1159
2 Cantó, C. *et al.* (2013) Crosstalk between poly(ADP-ribose) polymerase and sirtuin enzymes. *Mol. Aspects Med.* 34, 1168–1201
3 Hottiger, M.O. *et al.* (2010) Toward a unified nomenclature for mammalian ADP-ribosyltransferases. *Trends Biochem. Sci.* 35, 208–219
4 Leger, K. *et al.* (2014) ARTD2 activity is stimulated by RNA. *Nucleic Acids Res.* 42, 5072–5082
5 Feijs, K.L. *et al.* (2013) Macrodomain-containing proteins: regulating new intracellular functions of mono(ADP-ribosyl)ation. *Nat. Rev. Mol. Cell Biol.* 14, 443–451
6 Burkle, A. and Virag, L. (2013) Poly(ADP-ribose): PARadigms and PARadoxes. *Mol. Aspects Med.* 2, 00157–00154
7 De Vos, M. *et al.* (2012) The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. *Biochem. Pharmacol.* 84, 137–146
8 Rajamohan, S.B. *et al.* (2009) SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly (ADP-ribose) polymerase 1. *Mol. Cell. Biol.* 26, 4116–4129
9 Min, W. and Wang, Z.Q. (2009) Poly (ADP-ribose) glycohydrolase (PARG) and its therapeutic potential. *Front. Biosci. (Landmark Ed.)* 14, 1619–1626
10 Oka, S. *et al.* (2006) Identification and characterization of a mammalian 39-kDa poly(ADP-ribose) glycohydrolase. *J. Biol. Chem.* 281, 705–713
11 Mashimo, M. *et al.* (2013) ADP-ribosyl-acceptor hydrolase 3 regulates poly (ADP-ribose) degradation and cell death during oxidative stress. *Proc. Natl. Acad. Sci. U.S.A.* 110, 18964–18969
12 Formentini, L. *et al.* (2009) Poly(ADP-ribose) catabolism triggers AMP-dependent mitochondrial energy failure. *J. Biol. Chem.* 284, 17668–17676
13 Modis, K. *et al.* (2012) Cellular bioenergetics is regulated by PARP1 under resting conditions and during oxidative stress. *Biochem. Pharmacol.* 83, 633–643
14 Klaidman, L. *et al.* (2003) Nicotinamide offers multiple protective mechanisms in stroke as a precursor for NAD+, as a PARP inhibitor and by partial restoration of mitochondrial function. *Pharmacology* 69, 150–157
15 Zhou, H.Z. *et al.* (2006) Poly(ADP-ribose) polymerase-1 hyperactivation and impairment of mitochondrial respiratory chain complex I function in reperfused mouse hearts. *Am. J. Physiol. Heart Circ. Physiol.* 291, H714–H723
16 Virag, L. *et al.* (1998) Poly(ADP-ribose) synthetase activation mediates mitochondrial injury during oxidant-induced cell death. *J. Immunol.* 161, 3753–3759
17 Yu, S.W. *et al.* (2002) Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. *Science* 297, 259–263
18 Virag, L. and Szabo, C. (2002) The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. *Pharmacol. Rev.* 54, 375–429
19 Fang, E.F. *et al.* (2014) Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. *Cell* 157, 882–896
20 Cipriani, G. *et al.* (2005) Nuclear poly(ADP-ribose) polymerase-1 rapidly triggers mitochondrial dysfunction. *J. Biol. Chem.* 280, 17227–17234
21 Buonvicino, D. *et al.* (2013) Glucose deprivation converts poly(ADP-ribose) polymerase-1 hyperactivation into a transient energy producing process. *J. Biol. Chem.* 288, 36530–36537
22 Andrabi, S.A. *et al.* (2011) Iduna protects the brain from glutamate excitotoxicity and stroke by interfering with poly(ADP-ribose) polymer-induced cell death. *Nat. Med.* 17, 692–699
23 Gero, D. *et al.* (2014) Modulation of poly(ADP-ribose) polymerase-1 (PARP-1) mediated oxidative cell injury by ring finger protein 146 (RNF146) in cardiac myocytes. *Mol. Med.* 20, 313–328 http://dx.doi.org/10.2119/molmed.2014.00102
24 Andrabi, S.A. *et al.* (2014) Poly(ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis. *Proc. Natl. Acad. Sci. U.S.A.* 111, 10209–10214
25 Fouquerel, E. *et al.* (2014) ARTD1/PARP1 negatively regulates glycolysis by inhibiting hexokinase 1 independent of NAD depletion. *Cell Rep.* 10, 00712–00718
26 Krasnov, G.S. *et al.* (2013) Targeting VDAC-bound hexokinase II: a promising approach for concomitant anti-cancer therapy. *Expert Opin. Ther. Targets* 17, 1221–1233
27 Wang, Y. *et al.* (2011) Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). *Sci. Signal.* 4, 20
28 Niere, M. *et al.* (2012) ADP-ribosylhydrolase 3 (ARH3), not poly(ADP-ribose) glycohydrolase (PARG) isoforms, is responsible for degradation of mitochondrial matrix-associated poly(ADP-ribose). *J. Biol. Chem.* 287, 16088–16102
29 Pankotai, E. *et al.* (2009) Intra-mitochondrial poly(ADP-ribosyl)ation: potential role for alpha-ketoglutarate dehydrogenase. *Mitochondrion* 9, 159–164
30 Lai, Y. *et al.* (2008) Identification of poly-ADP-ribosylated mitochondrial proteins after traumatic brain injury. *J. Neurochem.* 104, 1700–1711
31 Druzhyna, N. *et al.* (2000) Poly(ADP-ribose) polymerase facilitates the repair of N-methylpurines in mitochondrial DNA. *Diabetes* 49, 1849–1855
32 Isabelle, M. *et al.* (2010) Investigation of PARP-1, PARP-2, and PARG interactomes by affinity-purification mass spectrometry. *Proteome Sci.* 8, 22
33 Niere, M. *et al.* (2008) Functional localization of two poly(ADP-ribose)-degrading enzymes to the mitochondrial matrix. *Mol. Cell. Biol.* 28, 814–824
34 Tapodi, A. *et al.* (2005) Pivotal role of Akt activation in mitochondrial protection and cell survival by poly(ADP-ribose)polymerase-1 inhibition in oxidative stress. *J. Biol. Chem.* 280, 35767–35775
35 Szanto, A. *et al.* (2009) PARP-1 inhibition-induced activation of PI-3-kinase–Akt pathway promotes resistance to taxol. *Biochem. Pharmacol.* 77, 1348–1357
36 Pinton, G. *et al.* (2013) PARP11 inhibition affects pleural mesothelioma cell viability and uncouples AKT/mTOR axis via SIRT1. *J. Cell. Mol. Med.* 17, 233–241
37 Yeh, T.Y. *et al.* (2006) Mitotic phosphorylation of tankyrase, a PARP that promotes spindle assembly, by GSK3. *Biochem. Biophys. Res. Commun.* 350, 574–579
38 Canto, C. *et al.* (2010) Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. *Cell Metab.* 11, 213–219
39 Ethier, C. *et al.* (2012) PARP-1 modulation of mTOR signaling in response to a DNA alkylating agent. *PLoS ONE* 7, e47978
40 Huang, Q. *et al.* (2009) A novel function of poly(ADP-ribose) polymerase-1 in modulation of autophagy and necrosis under oxidative stress. *Cell Death Differ.* 16, 264–277

41 Zhou, J. *et al.* (2012) AMPK mediates a pro-survival autophagy downstream of PARP-1 activation in response to DNA alkylating agents. *FEBS Lett.* 587, 170–177
42 Gongol, B. *et al.* (2013) AMPKalpha2 exerts its anti-inflammatory effects through PARP-1 and Bcl-6. *Proc. Natl. Acad. Sci. U.S.A.* 110, 3161–3166
43 Walker, J.W. *et al.* (2006) AMP-activated protein kinase is a positive regulator of poly(ADP-ribose) polymerase. *Biochem. Biophys. Res. Commun.* 342, 336–341
44 Bai, P. *et al.* (2011) PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. *Cell Metab.* 13, 461–468
45 Brenmoehl, J. and Hoeflich, A. (2013) Dual control of mitochondrial biogenesis by sirtuin 1 and sirtuin 3. *Mitochondrion* 13, 755–761
46 Mouchiroud, L. *et al.* (2013) The NAD(+)/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. *Cell* 154, 430–441
47 Cerutti, R. *et al.* (2014) NAD+-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. *Cell Metab.* 19, 1042–1049
48 Pirinen, E. *et al.* (2014) Pharmacological inhibition of poly(ADP–ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. *Cell Metab.* 19, 1034–1041
49 Huang, C.T. *et al.* (2013) Energy adaptive response during parthanatos is enhanced by PD98059 and involves mitochondrial function but not autophagy induction. *Biochim. Biophys. Acta* 1843, 531–543
50 Kim, S.H. *et al.* (2011) Neuronal Sirt3 protects against excitotoxic injury in mouse cortical neuron culture. *PLoS ONE* 6, e14731
51 Mohamed, J.S. *et al.* (2014) *MicroRNA-149* inhibits PARP-2 and promotes mitochondrial biogenesis via SIRT-1/PGC-1alpha network in skeletal muscle. *Diabetes* 63, 1546–1559
52 Bai, P. *et al.* (2011) PARP-2 regulates SIRT1 expression and whole-body energy expenditure. *Cell Metab.* 13, 450–460
53 Szanto, M. *et al.* (2011) Poly(ADP-ribose) polymerase-2 depletion reduces doxorubicin-induced damage through SIRT1 induction. *Cardiovasc. Res.* 92, 430–438
54 Geng, B. *et al.* (2013) *PARP-2* knockdown protects cardiomyocytes from hypertrophy via activation of SIRT1. *Biochem. Biophys. Res. Commun.* 430, 944–950
55 Diani-Moore, S. *et al.* (2010) Identification of the aryl hydrocarbon receptor target gene TiPARP as a mediator of suppression of hepatic gluconeogenesis by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and of nicotinamide as a corrective agent for this effect. *J. Biol. Chem.* 285, 38801–38810
56 Scarpulla, R.C. (2008) Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol. Rev.* 88, 611–638
57 Hossain, M.B. *et al.* (2009) Poly(ADP-ribose) polymerase 1 interacts with nuclear respiratory factor 1 (NRF-1) and plays a role in NRF-1 transcriptional regulation. *J. Biol. Chem.* 284, 8621–8632
58 Wu, T. *et al.* (2014) Poly(ADP-ribose) polymerase-1 modulates Nrf2-dependent transcription. *Free Radic. Biol. Med.* 67, 69–80
59 Zhang, H. *et al.* (2007) HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity. *Cancer Cell* 11, 407–420
60 Martin-Oliva, D. *et al.* (2006) Inhibition of poly(ADP-ribose) polymerase modulates tumor-related gene expression, including hypoxia-inducible factor-1 activation, during skin carcinogenesis. *Cancer Res.* 66, 5744–5756
61 Martinez-Romero, R. *et al.* (2008) PARP-1 modulates deferoxamine-induced HIF-1alpha accumulation through the regulation of nitric oxide and oxidative stress. *J. Cell. Biochem.* 104, 2248–2260
62 Martinez-Romero, R. *et al.* (2012) Nitric oxide modulates hypoxia-inducible factor-1 and poly(ADP-ribose) polymerase-1 cross talk in response to hypobaric hypoxia. *J. Appl. Physiol.* 112, 816–823
63 Canuelo, A. *et al.* (2011) The hypoxic preconditioning agent deferoxamine induces poly(ADP-ribose) polymerase-1-dependent inhibition of the mitochondrial respiratory chain. *Mol. Cell. Biochem.* 363, 816–823
64 Martinez-Romero, R. *et al.* (2009) Poly(ADP-ribose) polymerase-1 modulation of *in vivo* response of brain hypoxia-inducible factor-1 to hypoxia/reoxygenation is mediated by nitric oxide and factor inhibiting HIF. *J. Neurochem.* 111, 150–159
65 Scalia, M. *et al.* (2013) PARP-1 inhibitors DPQ and PJ-34 negatively modulate proinflammatory commitment of human glioblastoma cells. *Neurochem. Res.* 38, 50–58
66 Gonzalez-Flores, A. *et al.* (2013) Interaction between PARP-1 and HIF-2alpha in the hypoxic response. *Oncogene* 4, 9
67 Kraus, W.L. and Hottiger, M.O. (2013) PARP-1 and gene regulation: Progress and puzzles. *Mol. Aspects Med.* 34, 1109–1123
68 Mandir, A.S. *et al.* (2002) A novel *in vivo* post-translational modification of p53 by PARP-1 in MPTP-induced parkinsonism. *J. Neurochem.* 83, 186–192
69 Fatokun, A.A. *et al.* (2014) Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities. *Br. J. Pharmacol.* 171, 2000–2016
70 Pacher, P. *et al.* (2007) Nitric oxide and peroxynitrite in health and disease. *Physiol. Rev.* 87, 315–424
71 Robaszkiewicz, A. *et al.* (2014) The role of p38 signaling and poly(ADP-ribosyl)ation-induced metabolic collapse in the osteogenic differentiation-coupled cell death pathway. *Free Radic. Biol. Med.* 76C, 69–79
72 Bai, P. and Canto, C. (2012) The role of PARP-1 and PARP-2 enzymes in metabolic regulation and disease. *Cell Metab.* 16, 290–295
73 Nasrallah, C.M. and Horvath, T.L. (2014) Mitochondrial dynamics in the central regulation of metabolism. *Nat. Rev. Endocrinol.* 10, 650–658 http://dx.doi.org/10.1038/nrendo.2014.1160 Q9
74 Asher, G. *et al.* (2010) Poly(ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding. *Cell* 142, 943–953
75 Juvekar, A. *et al.* (2012) Combining a PI3K inhibitor with a PARP inhibitor provides an effective therapy for BRCA1-related breast cancer. *Cancer Discov.* 2, 1048–1063
76 Mangerich, A. *et al.* (2010) Inflammatory and age-related pathologies in mice with ectopic expression of human PARP-1. *Mech. Ageing Dev.* 131, 389–404
77 Bai, P. and Virag, L. (2012) Role of poly(ADP-ribose) polymerases in the regulation of inflammatory processes. *FEBS Lett.* 586, 3771–3777
78 DeBerardinis, R.J. *et al.* (2008) The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* 7, 11–20
79 Green, D.R. *et al.* (2014) Cell biology. Metabolic control of cell death. *Science* 19 http://dx.doi.org/10.1126/science.1250256 345 (6203) 1250256 Q10
80 Curtin, N. and Szabo, C. (2013) Therapeutic applications of PARP inhibitors: anticancer therapy and beyond. *Mol. Aspects Med.* 6, 1043–1258
81 Michels, J. *et al.* (2014) PARP and other prospective targets for poisoning cancer cell metabolism. *Biochem. Pharmacol.* 5, 00516–00514
82 Gonzalez-Billalabeitia, E. *et al.* (2014) Vulnerabilities of PTEN–TP53-deficient prostate cancers to compound PARP–PI3K inhibition. *Cancer Discov.* 4, 896–904
83 Mohamed, J.S. *et al.* (2014) Dysregulation of SIRT-1 in aging mice increases skeletal muscle fatigue by a PARP-1-dependent mechanism. *Aging (Albany NY)* 6, 820–834
84 Pacher, P. *et al.* (2004) A new, potent poly(ADP-ribose) polymerase inhibitor improves cardiac and vascular dysfunction associated with advanced aging. *J. Pharmacol. Exp. Ther.* 311, 485–491
85 Mukhopadhyay, P. *et al.* (2014) Poly (ADP-ribose) polymerase-1 is a key mediator of liver inflammation and fibrosis. *Hepatology* 59, 1998–2009
86 Alaynick, W.A. (2008) Nuclear receptors, mitochondria and lipid metabolism. *Mitochondrion* 8, 329–337
87 Szanto, M. *et al.* (2012) Poly(ADP-ribose) polymerase-2: emerging transcriptional roles of a DNA repair protein. *Cell. Mol. Life Sci.* 69, 4079–4092