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# Poly-(ADP-ribose) Polymerases and Mitochondria

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## ABSTRACT

Mitochondrial function is crucial to respond adequately to extracellular stress stimuli that is regulated by a complex network of signal transduction pathways. Poly (ADP-ribose) polymerase (PARP) activation has been shown to hamper mitochondrial activity and certain pathologies associated with mitochondrial dysfunction are advanced by PARP activation. Recent studies have shown that PARP inhibition leads to mitochondrial biogenesis. However, there are still many open questions about the role of PARPs in mitochondrial regulation, such as the existence of intra-mitochondrial PARP activity or the involvement of mitotropic factors. Hereby, we give an overview of our current knowledge on the impact of PARPs on mitochondrial processes with special attention to these debated issues and the practical applicability of PARP inhibition to treat diseases associated with mitochondrial dysfunction.

## PARPS AND PARYLATION

Poly (ADP-ribose) polymerases (PARPs) or diphtheria toxin-type ADP-ribose transferases (ARTDs) are multidomain proteins composing a protein family of 17 members in humans and 16 in mice [1]. PARPs are predominantly nuclear enzymes, originally identified as DNA repair factors,

but now it is evident that there is more than that about PARPs. PARPs are involved in numerous cellular processes that are vital for the maintenance of cellular homeostasis. The majority of these processes are related to cellular stress response [2], such as the regulation of cell death in oxidative stress-related pathologies, as well as metabolic, immune and transcriptional regulation [3]. PARP enzymes are composed of functionally distinct domains sharing an evolutionarily conserved catalytic domain that shows structural homology to other ADP-ribosyl transferase proteins [4-6]. Besides, other domains of PARPs are responsible for protein-protein interactions, protein-nucleic acid interactions, and protein-metabolite interactions [5,6].

Activated PARPs bind and cleave substrate $NAD^+$ into nicotinamide and ADP-ribose (ADPR) then covalently attach one or more ADPR units to themselves or other acceptors performing mono-, oligo- or poly (ADP-ribosyl)ation (PARylation) [2]. PARylation is an evolutionarily conserved posttranslational modification of proteins that may alter the conformation of acceptors or disrupt protein–nucleic acid and protein–protein interactions, hence PARylation impacts the biochemical or physiological properties of proteins [2]. PARP-1 constitutes the major PARP activity of cells (85-90%), followed by PARP-2 with 10-15% [7], while the other PARPs show insignificant contribution. The first recognized triggers of PARP activation were single or double strand breaks in DNA [4]. PARP-1, PARP-2 and PARP-3 are indeed activated by DNA damage, however, the activity of these PARPs is also influenced by posttranslational modifications and signal transduction pathways [3,4,8,9]. PAR has a short half-life since it is rapidly degraded to ADPR by enzymes such as poly (ADP-ribose) glycohydrolase (PARG) that can cleave the bonds of the PAR polymer. There are different PARG isoforms in most cellular compartments [10]. Furthermore, PAR levels in the cells are also regulated by ADP-ribosyl acceptor hydrolase 3 (ARH3), ADP-ribosyl lyase and macrodomain-containing proteins [4,6,10,11].

## EFFECTS OF PARP ACTIVATION ON MITOCHONDRIAL FUNCTION

Regulation of mitochondrial activity is carried out by a complicated network of signal transduction pathways that determine mitochondrial adaptation to stress, therefore these pathways are crucial for cell survival. PARP-1 and PARP-2 have been shown to interfere with mitochondrial activity in response to oxidative stress or nutrient availability.

PARP activation (mostly exerted by PARP-1) hampers mitochondrial oxygen consumption and discharges mitochondrial membrane potential [12,13]. PARP-1 activation leads to electron transport chain uncoupling and superoxide production [13] by reducing the activity of mitochondrial complex I [14], NADH-oxidase, and NADH Q1-reductase [15]. As a result, mitochondrial architecture becomes disorganized and mitochondrial transition pores (MTPs) open [13]. Subsequently, molecules such as cardiolipin, apoptosis inducing factor (AIF), cytochrome c or caspases escape mitochondria [13,16,17]. Mitophagy, a process during which damaged portions of the mitochondria are eliminated, is also negatively affected by PARP-1 activation [18]. PARP activation depletes cellular $NAD^+$ and ATP levels, thus leading to mitochondrial energy

catastrophe. ATP levels were supposed to be reduced as a result of the cells' attempt to replenish $NAD^+$ through the energy intensive function of nicotinamide mononucleotide adenylyltransferase (NMNAT) and phosphoribosyl pyrophosphate synthetase (PPS) [17]. However, there are other theories that may explain the reduction in ATP upon PARP activation. For example, NUDIX pyrophosphatases can convert ADPR, the end product of PAR hydrolysis, to AMP [19]. Increases in AMP levels block mitochondrial adenine nucleotide translocator (ANT) [19] preventing ATP disposal. Furthermore, PARP-1 overactivation limits ADP availability, therefore adenylate kinase capacity to synthesize ATP from ADP is hampered [20].

PAR may be present outside the nucleus, where PAR can bind to mitochondria and induce mitochondrial dysfunction and cell death [21]. According to recent findings, this can be prevented by Iduna, a cytoplasmic E3-ubiquitin ligase which binds the PAR polymer and thereby provides protection against PAR-induced mitochondrial damage [21]. Moreover, Iduna contributes to the cytoplasmic degradation of PARylated proteins (PARP-1 or other) by directing them to the proteasome [22]. Hexokinase (HK) is essential in maintaining the coupling between glycolysis and mitochondrial oxidation [23]. PAR binding to HK leads to the release of HK from the mitochondrial surface disrupting the coupling of glycolysis and mitochondrial oxidation [24,25]. Finally, it is of note that the release of the cell death inducer AIF from the mitochondria requires the binding of PAR to AIF [26].

HIF-1 and HIF-2 promote the adaptation to hypoxia by triggering transcriptional programs involved in the regulation anaerobic metabolic pathways (such as glycolysis), while inhibiting oxygen dependent mitochondrial oxidation [27]. It has been reported that HIF1-mediated inhibition of mitochondrial complex II and IV in deferoxamine-induced hypoxia requires PARP-1 activation [28] and PARP-1-induced free radical production [29,30,31]. PARP-1 inhibition suppresses HIF-1 activation [30,32]. PARP-1 also interacts with HIF-2 and facilitates the expression of genes regulated by HIF-2 [33]. Taken together, PARP-1 activation promotes the activation of HIF-1 and HIF-2 supporting the downregulation of mitochondrial activity.

## INTRAMITOCHONDRIAL PARP ACTIVITY AS A NEGATIVE REGULATOR OF MITOCHONDRIAL FUNCTION

PARP activity may exist inside the mitochondria, however, it has been a long-debated issue. Nevertheless, there is consensus about the presence of PAR-degrading activity in mitochondria that is mostly attributed to ARH3 [34]. There are early reports identifying PARylated proteins in isolated rat liver mitochondria [35,36] that are highly debated. It is of note though, that the different studies [35,36] did not agree in the proteins identified with a PAR antibody, therefore further investigations are needed to verify these findings.

Despite the fact that intramitochondrial PARylation is not accepted widely, it is clear that overexpression of PARP-1 in mitochondria leads to increased mitochondrial PARylation

accompanied by decreased mitochondrial output, but preserved glycolytic flux [34]. Taken together, additional data is required to determine the presence of mitochondrial PARP activity. However, it seems that PARylation of mitochondrial proteins have a profound negative effect on mitochondrial oxidative phosphorylation and probably affect $NAD^+$ levels inside the mitochondria and consequently the activity of mitochondrial $NAD^+$-dependent enzymes.

Nonetheless, it is worth mentioning recent research evidence pointing towards the existence of mitochondrial PARP-1 that is probably a key regulator of cellular processes and is catalytically activated by DNA damage. These provocative results show that despite the originally described concept, 10 minutes after $H_2O_2$ exposure in human monocytes PARP-1 activation occurs exclusively in mitochondria and nuclear PARylation follows only later [37]. Moreover, the authors explored that phosphorylation by protein kinase A (PKA) regulates mitochondrial PARP-1 activity in early stage of oxidative stress as a result of a β-adrenoreceptor signaling. Intramitochondrial PARP-1 activation coincided with damage in mitochondrial DNA [37]. The gradual increase in oxidative injury and PARP-1 activity results in mitochondrial electron transport defect and mitochondrial dysfunction and cell death within 24 hours after exposure [37].

As mentioned previously, PARP-1 is a DNA repair protein that facilitates nuclear DNA repair by recognizing DNA strand breaks and promotes the recruitment of DNA repair enzymes to the damaged DNA sequences. It is an intriguing question that whether intramitochondrial PARP-1 activity plays a similar role in the repair of mitochondrial DNA. In a recent study Szczesny et al. [38] went after this question and found that mitochondrial PARP-1 interacts with two DNA base excision repair (BER) enzymes (EXOG and DNA polymerase gamma) which are localized inside the mitochondria. This interaction exists under normal conditions, but oxidative stress induced a marked increase in the PARylation of these mitochondrial DNA repair enzymes. However, PARylation negatively affected their capacity in the repair of mitochondrial DNA and therefore in the maintenance of mitochondrial DNA integrity. Taken together, this study demonstrated a striking phenomenon that in contrast to the pivotal positive role that PARP-1 represents in nuclear DNA repair, mitochondrial PARP-1 is a negative regulator of mitochondrial DNA repair thus mitochondrial DNA integrity. Since mitochondrial DNA integrity affects mitochondrial protein transcription and mitochondrial homeostasis [39,40], PARP-1 may also act as a regulator of these functional mitochondrial processes. The fact that PARP inhibition induces the mitochondrial sirtuin, SIRT3, also point towards the existence of a major $NAD^+$-consuming, possibly PARP activity in mitochondria [41]. Table 1 summarizes the known mitochondrial proteins interacting with PARPs.

**Table 1:** Mitochondrial proteins interacting with members of the PARP family.

| Name | Interaction | PARylation | Reference |
|---|---|---|---|
| ATP synthase subunit beta, mitochondrial | PARP-2 | ? | [42] |
| CPS gi | PARP-1? | X | [35] |
| Cytochrome c oxidase subunit Va | PARP-1 ? | X | [36] |
| dihydrolipoamide dehydrogenase | PARP-1 ? | X | [35] |
| F1F0 ATPase, b subunit | PARP-1 ? | X | [36] |
| F1F0 ATPase, g subunit | PARP-1 ? | X | [35] |
| L-lactate dehydrogenase | PARP-1 | ? | [42] |
| Malate dehydrogenase, mitochondrial | PARP-1 | ? | [42] |
| Mitofilin (mitochondrial inner membrane protein) | PARP-1 ? | X | [36] |
| OTC hi | PARP-1? | X | [35] |
| Voltage-dependent anion channel-1 | PARP-1 ? | X | [36] |
| 75 kDa Glucose regulated protein / mitochondrial heat-shock protein-70 | PARP-1 ? | X | [36] |
| 60 kDa Heat-shock protein / mitochondrial precursor 60 kDa chaperone | PARP-1 ? | X | [36] |
| EXOG | PARP-1 | X | [38] |
| DNA polymerase γ | PARP-1 | X | [38] |

## POSITIVE PARP-MEDIATED REGULATORS OF MITOCHONDRIAL ACTIVITY

Signal transduction pathways react to environmental stimuli and translate them into mitochondrial regulation. PARP-1 is known to modulate the action of the phosphatidyl-inositol 3-kinase (PI3K)–Akt–glycogen synthase kinase-3 (GSK3) and AMP activated kinase (AMPK) pathways [43]. It has been shown that PARP inhibition preserves mitochondrial membrane potential under stress conditions [43] by increasing the activity of PI3K [44] and Akt [43-45]. Besides, PARP-1 activation enhances the activity of the energy sensor AMPK [46-48], thereby inducing mitochondrial function and facilitating autophagy [46,47].

PARPs can also regulate mitochondrial function through modulating transcription. Human sirtuins (SIRT1–7) are $NAD^+$-dependent protein deacetylases [49]. Therefore a decrease in cellular $NAD^+$/NADH ratio can activate sirtuins [4,49]. PARPs have been shown to modulate nuclear SIRT1 and the mitochondrial SIRT3 action. Activation of both sirtuins boost mitochondrial activity by deacetylating target proteins involved in mitochondrial function. SIRT1 activation leads to a more efficient mitophagy, mitochondrial unfolded protein response and, as a result, the preservation of mitonuclear protein balance [50]. SIRT1 and PARP-1 compete for the same $NAD^+$ pool. PARP-1 shows higher affinity for $NAD^+$ as compared to SIRT1, therefore PARP-1 activation can limit SIRT1 activity [4]. Hence, depletion or genetic deletion of PARP-1 increases nuclear $NAD^+$ levels [51-53], that results in enhanced SIRT1 activity and better mitochondrial output, improved performance of

the mitochondrial unfolded protein response and mitonuclear protein balance in skeletal muscle and brown adipose tissue [53]. In turn, SIRT1 can deacetylate and hence inhibit PARP-1 [4].

Another PARP, PARP-2 also impacts SIRT1 activity. Silencing or deletion of PARP-2 resulted in enhanced SIRT1 activity and therefore increased mitochondrial biogenesis in multiple in vitro studies [54-57].

Activation of NRF-1 and NRF-2 results in increased mitochondrial activity by inducing the expression of such important mitochondrial genes as cytochrome c and mitochondrial transcription factor A [58]. To do so, NRFs interact with cofactors PGC-1α and PGC-1β and bind to its consensus DNA sequences called antioxidant response elements [58]. PARP-1 forms a complex with NRF1 by binding to and PARylating the DNA binding domain of NRF1 [59]. This complex binds to the promoter region of the human cytochrome c gene and promotes cytochrome c expression [59]. Besides, PARP-1 has also been reported to act as a transcriptional coactivator for NRF-2 [60].

## MITOCHONDRIAL DISEASES MEDIATED BY PARPs

In case of diseases associated with mitochondrial damage, boosting of mitochondrial biogenesis is a therapeutic option that stabilizes mitochondrial energy production and restores mitochondrial biosynthetic pathways. As mentioned previously, PARP activation has a negative effect on mitochondrial function, therefore several pathologies associated with mitochondrial dysfunction are concomitant with or advanced by PARP activation. Hence, pharmacological inhibition or genetic deletion of PARP-1 or PARP-2 alleviates mitochondrial dysfunction thereby provides protection against these pathologies. DNA damage-induced PARP activation followed by mitochondrial dysfunction and cell death underlies several diseases primarily through determining the mode of cell death (apoptosis, necrosis or parthanatos) [2].

PARP activation is also a significant feature in diseases associated with mild, however long-term mitochondrial dysfunction. There is a strong likelihood that the impairment of PARP-mediated pathways contribute to the pathogenesis of metabolic disorders, cancer, and aging. Moreover, PARP-1 is implicated in metabolic regulation, wherein it mediates central and peripheral circadian rhythm oscillations and the function of endocrine glands (e.g. pancreas) or it is involved in the signal transduction events following hormone action (e.g. incretins) [2,61].

## PERSPECTIVES

PARP activation interferes with several pathways that impact on mitochondrial function, and seems to contribute to the pathology of numerous diseases. These diseases involve metabolic dysfunctions, aging and even cancer, all of which represent a huge public health issue. Therefore, a better understanding of the connection of PARPs and mitochondria promises therapeutic potential and calls for further investigation.

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## References


1. Hottiger MO, Hassa PO, Lüscher B, Schüler H, Koch-Nolte F. Toward a unified nomenclature for mammalian ADP-ribosyltransferases. Trends Biochem Sci. 2010; 35: 208-219.
2. Bai P. Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance. Mol Cell. 2015; 58: 947-958.
3. Bürkle A, Virág L. Poly(ADP-ribose): PARadigms and PARadoxes. Mol Aspects Med. 2013; 34: 1046-1065.
4. Cantó C, Sauve AA, Bai P. Crosstalk between poly(ADP-ribose) polymerase and sirtuin enzymes. Mol Aspects Med. 2013; 34: 1168-1201.
5. Léger K, Bär D, Savić N, Santoro R, Hottiger MO. ARTD2 activity is stimulated by RNA. Nucleic Acids Res. 2014; 42: 5072-5082.
6. Feijs KL, Forst AH, Verheugd P, Lüscher B. Macrodomain-containing proteins: regulating new intracellular functions of mono(ADP-ribosyl)ation. Nat Rev Mol Cell Biol. 2013; 14: 443-451.
7. Szántó M, Brunyánszki A, Kiss B, Nagy L, Gergely P. Poly(ADP-ribose) polymerase-2: emerging transcriptional roles of a DNA-repair protein. Cell Mol Life Sci. 2012; 69: 4079-4092.
8. Sajish M, Schimmel P. A human tRNA synthetase is a potent PARP1-activating effector target for resveratrol. Nature. 2015; 519: 370-373.
9. Rajamohan SB, Pillai VB, Gupta M, Sundaresan NR, Birukov KG. SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. Mol Cell Biol. 2009; 29: 4116-4129.
10. Min W, Wang ZQ. Poly (ADP-ribose) glycohydrolase (PARG) and its therapeutic potential. Front Biosci (Landmark Ed). 2009; 14: 1619-1626.
11. Niere M, Mashimo M, Agledal L, Dölle C, Kasamatsu A. 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. 2012; 287: 16088-16102.
12. Módis K, Gero D, Erdélyi K, Szoleczky P, DeWitt D. Cellular bioenergetics is regulated by PARP1 under resting conditions and during oxidative stress. Biochem Pharmacol. 2012; 83: 633-643.
13. Virág L, Salzman AL, Szabó C. Poly(ADP-ribose) synthetase activation mediates mitochondrial injury during oxidant-induced cell death. J Immunol. 1998; 161: 3753-3759.
14. Klaidman L, Morales M, Kem S, Yang J, Chang ML, et al. Nicotinamide offers multiple protective mechanisms in stroke as a precursor for NAD+, as a PARP inhibitor and by partial restoration of mitochondrial function. Pharmacology. 2003; 69: 150-157.
15. Zhou HZ, Swanson RA, Simonis U, Ma X, Cecchini G. 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. 2006; 291: H714-723.
16. Yu SW, Wang H, Poitras MF, Coombs C, Bowers WJ. Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science. 2002; 297: 259-263.
17. Virág L, Szabó C. The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. Pharmacol Rev. 2002; 54: 375-429.
18. Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. Cell. 2014; 157: 882-896.
19. Formentini L, Macchiarulo A, Cipriani G, Camaioni E, Rapizzi E. Poly(ADP-ribose) catabolism triggers AMP-dependent mitochondrial energy failure. J Biol Chem. 2009; 284: 17668-17676.
20. Buonvicino D, Formentini L, Cipriani G, Chiarugi A. Glucose deprivation converts poly(ADP-ribose) polymerase-1 hyperactivation into a transient energy-producing process. J Biol Chem. 2013; 288: 36530-36537.
21. Andrabi SA, Kang HC, Haince JF, Lee YI, Zhang J. Iduna protects the brain from glutamate excitotoxicity and stroke by interfering with poly(ADP-ribose) polymer-induced cell death. Nat Med. 2011; 17: 692-699.

22. Gerö D, Szoleczky P, Chatzianastasiou A, Papapetropoulos A2, Szabo C1. Modulation of poly(ADP-ribose) polymerase-1 (PARP-1)-mediated oxidative cell injury by ring finger protein 146 (RNF146) in cardiac myocytes. Mol Med. 2014; 20: 313-328.

23. Krasnov GS, Dmitriev AA, Lakunina VA, Kirpiy AA, Kudryavtseva AV. Targeting VDAC-bound hexokinase II: a promising approach for concomitant anti-cancer therapy. Expert Opin Ther Targets. 2013; 17: 1221-1233.

24. Andrabi SA, Umanah GK, Chang C, Stevens DA, Karuppagounder SS. Poly(ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis. Proc Natl Acad Sci U S A. 2014; 111: 10209-10214.

25. Fouquerel E, Goellner EM, Yu Z, Gagné JP, Barbi de Moura M. ARTD1/PARP1 negatively regulates glycolysis by inhibiting hexokinase 1 independent of NAD+ depletion. Cell Rep. 2014; 8: 1819-1831.

26. Wang Y, Kim NS, Haince JF, Kang HC, David KK. Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). Sci Signal. 2011; 4: ra20.

27. Zhang H, Gao P, Fukuda R, Kumar G, Krishnamachary B. HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity. Cancer Cell. 2007; 11: 407-420.

28. Martin-Oliva D, Aguilar-Quesada R, O'valle F, Muñoz-Gámez JA, Martínez-Romero R, et al. Inhibition of poly(ADP-ribose) polymerase modulates tumor-related gene expression, including hypoxia-inducible factor-1 activation, during skin carcinogenesis. Cancer Res. 2006; 66: 5744-5756.

29. Martínez-Romero R, Martínez-Lara E, Aguilar-Quesada R, Peralta A, Oliver FJ. PARP-1 modulates deferoxamine-induced HIF-1alpha accumulation through the regulation of nitric oxide and oxidative stress. J Cell Biochem. 2008; 104: 2248-2260.

30. Martínez-Romero R, Cañuelo A, Martínez-Lara E, Javier Oliver F, Cárdenas S. 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. 2009; 111: 150-159.

31. Cañuelo A, Martínez-Romero R, Martínez-Lara E, Sánchez-Alcázar JA, Siles E. The hypoxic preconditioning agent deferoxamine induces poly(ADP-ribose) polymerase-1-dependent inhibition of the mitochondrial respiratory chain. Mol. Cell. Biochem. 2011; 363: 816-823.

32. Scalia M, Satriano C, Greca R, Stella AM, Rizzarelli E. PARP-1 inhibitors DPQ and PJ-34 negatively modulate proinflammatory commitment of human glioblastoma cells. Neurochem Res. 2013; 38: 50-58.

33. Gonzalez-Flores A, Aguilar-Quesada R, Siles E, Pozo S, Rodríguez-Lara MI. Interaction between PARP-1 and HIF-2(alpha) in the hypoxic response. Oncogene. 2014; 33: 891-898.

34. Niere M, Kernstock S, Koch-Nolte F, Ziegler M. Functional localization of two poly(ADP-ribose)-degrading enzymes to the mitochondrial matrix. Mol Cell Biol. 2008; 28: 814-824.

35. Pankotai E, Lacza Z, Murányi M, Szabó C. Intra-mitochondrial poly(ADP-ribosyl)ation: potential role for alpha-ketoglutarate dehydrogenase. Mitochondrion. 2009; 9: 159-164.

36. Lai Y, Chen Y, Watkins SC, Nathaniel PD, Guo F. Identification of poly-ADP-ribosylated mitochondrial proteins after traumatic brain injury. J Neurochem. 2008; 104: 1700-1711.

37. Brunyanszki A, Olah G, Coletta C, Szczesny B, Szabo C. Regulation of mitochondrial poly(ADP-Ribose) polymerase activation by the (beta) adrenoceptor/cAMP/protein kinase A axis during oxidative stress. Mol Pharmacol. 2014; 86: 450-462.

38. Szczesny B, Brunyanszki A, Olah G, Mitra S, Szabo C. Opposing roles of mitochondrial and nuclear PARP1 in the regulation of mitochondrial and nuclear DNA integrity: implications for the regulation of mitochondrial function. Nucleic Acids Res. 2014; 42: 13161-13173.

39. Cline SD. Mitochondrial DNA damage and its consequences for mitochondrial gene expression. Biochim Biophys Acta. 2012; 1819: 979-991.

40. Berneburg M, Kamenisch Y, Krutmann J, Röcken M. 'To repair or not to repair - no longer a question': repair of mitochondrial DNA shielding against age and cancer. Exp Dermatol. 2006; 15: 1005-1015.

41. Kim SH, Lu HF, Alano CC. Neuronal Sirt3 protects against excitotoxic injury in mouse cortical neuron culture. PLoS One. 2011; 6: e14731.

42. Isabelle M, Moreel X, Gagné JP, Rouleau M, Ethier C. Investigation of PARP-, PARP-2, and PARG interactomes by affinity-purification mass spectrometry. Proteome Sci. 2010; 8: 22.

43. Tapodi A, Debreceni B, Hanto K, Bognar Z, Wittmann I. Pivotal role of Akt activation in mitochondrial protection and cell survival by poly(ADP-ribose)polymerase-1 inhibition in oxidative stress. J Biol Chem. 2005; 280: 35767-35775.

44. Szanto A, Hellebrand EE, Bognar Z, Tucsek Z, Szabo A. PARP-1 inhibition-induced activation of PI-3-kinase-Akt pathway promotes resistance to taxol. Biochem Pharmacol. 2009; 77: 1348-1357.

45. Pinton G, Manente AG, Murer B, De Marino E, Mutti L. PARP1 inhibition affects pleural mesothelioma cell viability and uncouples AKT/mTOR axis via SIRT1. J Cell Mol Med. 2013; 17: 233-241.

46. Ethier C, Tardif M, Arul L, Poirier GG. PARP-1 modulation of mTOR signaling in response to a DNA alkylating agent. PLoS One. 2012; 7: e47978.

47. Huang Q, Wu YT, Tan HL, Ong CN, Shen HM. A novel function of poly(ADP-ribose) polymerase-1 in modulation of autophagy and necrosis under oxidative stress. Cell Death Differ. 2009; 16: 264-277.

48. Zhou J, Ng S, Huang Q, Wu YT, Li Z. AMPK mediates a pro-survival autophagy downstream of PARP-1 activation in response to DNA alkylating agents. FEBS Lett. 2013; 587: 170-177.

49. Brenmoehl J, Hoeflich A. Dual control of mitochondrial biogenesis by sirtuin 1 and sirtuin 3. Mitochondrion. 2013; 13: 755-761.

50. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D. The NAD(+)/Sirtuin Pathway Modulates Longevity through Activation of Mitochondrial UPR and FOXO Signaling. Cell. 2013; 154: 430-441.

51. Bai P, Canto C, Brunyánszki A, Huber A, Szántó M. PARP-2 regulates SIRT1 expression and whole-body energy expenditure. Cell Metab. 2011; 13: 450-460.

52. Cerutti R, Pirinen E, Lamperti C, Marchet S, Sauve AA. NAD(+)-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. Cell Metab. 2014; 19: 1042-1049.

53. Pirinen E, Cantó C, Jo YS, Morato L, Zhang H. Pharmacological Inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. Cell Metab. 2014; 19: 1034-1041.

54. Mohamed JS, Hajira A, Pardo PS, Boriek AM. MicroRNA-149 inhibits PARP-2 and promotes mitochondrial biogenesis via SIRT-1/PGC-1(alpha) network in skeletal muscle. Diabetes. 2014; 63: 1546-1559.

55. Bai P, Cantó C, Oudart H, Brunyánszki A, Cen Y, et al. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell Metab. 2011; 13: 461-468.

56. Szántó M, Rutkai I, Hegedus C, Czikora Á, Rózsahegyi M. Poly(ADP-ribose) polymerase-2 depletion reduces doxorubicin-induced damage through SIRT1 induction. Cardiovasc Res. 2011; 92: 430-438.

57. Geng B, Cai Y, Gao S, Lu J, Zhang L. PARP-2 knockdown protects cardiomyocytes from hypertrophy via activation of SIRT1. Biochem Biophys Res Commun. 2013; 430: 944-950.

58. Scarpulla RC. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev. 2008; 88: 611-638.

59. Hossain MB, Ji P, Anish R, Jacobson RH, Takada S. 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. 2009; 284: 8621-8632.

60. Wu T, Wang XJ, Tian W, Jaramillo MC, Lau A. Poly(ADP-ribose) polymerase-1 modulates Nrf2-dependent transcription. Free Radic Biol Med. 2014; 67: 69-80.

61. Bai P, Cantó C. The role of PARP-1 and PARP-2 enzymes in metabolic regulation and disease. Cell Metab. 2012; 16: 290-295.