

Accepted Manuscript



Title: Metabolic roles of poly(ADP-ribose) polymerases

Author: András Vida Judit Márton Edit Mikó Péter Bai

PII: S1084-9521(16)30493-1

DOI: <http://dx.doi.org/doi:10.1016/j.semcdb.2016.12.009>

Reference: YSCDB 2179

To appear in: *Seminars in Cell & Developmental Biology*

Received date: 30-6-2016

Accepted date: 20-12-2016

Please cite this article as: Vida András, Márton Judit, Mikó Edit, Bai Péter. Metabolic roles of poly(ADP-ribose) polymerases. *Seminars in Cell and Developmental Biology* <http://dx.doi.org/10.1016/j.semcdb.2016.12.009>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Metabolic roles of poly(ADP-ribose) polymerases

András Vida^{1,2,#}, Judit Márton^{1,#}, Edit Mikó^{1,2}, Péter Bai^{1,2,3,*}

¹Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, 4032, Hungary;

²MTA-DE Lendület Laboratory of Cellular Metabolism Research Group, Debrecen, H-4032, Hungary;

³Research Center for Molecular Medicine, Faculty of Medicine University of Debrecen, 4032, Hungary;

#equal contribution

*Address correspondence to this author at the Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, H- 4032 Debrecen, Egyetem tér 1, Hungary; Tel: +36 52 412 345; Fax: +36 52 412 566; E-mail: baip@med.unideb.hu

Contents

1.	The biochemistry and enzymology of PARPs	7
2.	PARPs in the transcriptional regulation of metabolism	8
2.1	PARPs and Sirtuins	8
2.2	PARPs and nuclear receptors	9
2.3	PARP-2 and sterol-regulated element binding proteins (SREBPs).....	10
2.4	Interaction of PARPs with other metabolic transcription factors	10
3	Relationship of PARPs and energy sensor systems.....	11
4	Interplay of PARPs with mitochondrial homeostasis.....	11
5	PARPs in higher order metabolic regulation	13
5.1	Regulatory role of PARPs in lipid metabolism.....	13
5.2	PARPs and circadian rhythm, food uptake and hormonal control	14
5.2.1.	Role of PARPs in circadian rhythm control	14
5.2.2.	PARPs in the regulation of glucose homeostasis.....	14
5.2.3.	PARPs and other metabolic hormones	15
6	PARP-mediated metabolic diseases.....	15
7	Conclusions	16

Highlights

- PARP enzymes regulate metabolic transcription factors and energy sensor systems.
- PARP-1 and PARP-2 regulate mitochondrial oxidation.
- PARPs are involved in higher order metabolic regulation and in the pathogenesis of metabolic diseases.

Abstract

Poly(ADP-ribosyl)ation (PARylation) is an evolutionarily conserved reaction that had been associated with numerous cellular processes such as DNA repair, protein turnover, inflammatory regulation, aging or metabolic regulation. The metabolic regulatory tasks of poly(ADP-ribose) polymerases (PARPs) are complex, it is based on the regulation of metabolic transcription factors (e.g. SIRT1, nuclear receptors, SREBPs) and certain cellular energy sensors. PARP over-activation can cause damage to mitochondrial terminal oxidation, while the inhibition of PARP-1 or PARP-2 can induce mitochondrial oxidation by enhancing the mitotropic tone of gene transcription and signal transduction. These PARP-mediated processes impact on higher order metabolic regulation that modulates lipid metabolism, circadian oscillations and insulin secretion and signaling. PARP-1, PARP-2 and PARP-7 are related to metabolic diseases such as diabetes, alcoholic and non-alcoholic fatty liver disease (AFLD, NAFLD), or on a broader perspective to Warburg metabolism in cancer or the metabolic diseases accompanying aging.

Abbreviations

ABCA1	ATP-binding cassette sub-family A Member 1
ACACA	Acetyl-CoA Carboxylase Alpha
ACBD3	Acyl-CoA Binding Domain Containing 3
ACLY	ATP Citrate Lyase
ADP	Adenosine Diphosphate
ADPR	ADP-ribose
AFLD	Alcoholic Fatty Liver Disease
AIF	Apoptosis Inducing Factor
AMPK	AMP activated kinase
ANT	Adenine Nucleotide Translocase
ARH3	ADP-ribosylhydrolase 3
CLOCK	Circadian Locomotor Output Cycles Kaput
CRY	Cryptochrome Circadian Clock
DNA	Deoxyribonucleic Acid
EPHX1	Microsomal Epoxide Hydrolase
ER	Estrogen Receptor
ERK	Extracellular Signal-regulated Kinase
FA	Fatty Acid
FASN	Fatty Acid Synthase
FDPS	Farnesyl Diphosphate Synthase
FOXO1	Forkhead Box Protein O1
GLP-1	Glucagon-like Peptide-1
GSK3	Glycogen Synthase Kinase-3
HIF	Hypoxia-inducible Factor
HMGCR	3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase
HMGCS	3-Hydroxy-3-Methylglutaryl-Coenzyme A Synthase
LDLR	Low Density Lipoprotein Receptor
LXR	Liver X Receptor
ME2	Malic Enzyme 2
miRNA	Micro-Ribonucleic Acid
mTOR	Mechanistic Target of Rapamycin
MTP	Mitochondrial Transition Pore
NAD	Nicotinamide Adenine Dinucleotide
NAFLD	Non-Alcoholic Fatty Liver Disease
NOR-1	Neuron-derived Orphan Receptor 1
NR4A	Nuclear Receptor Subfamily 4 Group A
NRF	Nuclear Respiratory Factor

NUDIX	Nucleoside Diphosphate Linked to X
PAR	poly(ADP-ribose)
PARG	poly(ADP-ribose) Glycohydrolase
PARP	poly(ADP-ribose) Polymerase
PARPi	poly(ADP-ribose) Polymerase Inhibitor
PARylation	poly(ADP-ribosyl)ation
PDX-1	Pancreatic And Duodenal Homeobox 1
PER	Period Circadian Clock
PGC-1 α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome Proliferators Activated Receptor
PR	Progesterone Receptor
RAR	Retinoic Acid Receptor
RNA	Ribonucleic Acid
RXR	Retinoic X Receptor
SCD	Stearoyl-CoA Desaturase (Delta-9-Desaturase)
SIRT	Sirtuin
SREBP	Sterol-regulated Element Binding Proteins
TG	Triglyceride
TNK1	Tyrosine Kinase Non Receptor 1
TR	Thyroid Hormone Receptor
WAT	White Adipose Tissue

Keywords: PARP, ARTD, metabolism, mitochondria, diabetes, obesity

1. The biochemistry and enzymology of PARPs

Seventeen multidomain proteins belong to the PARP family in humans, all members share the PARP domain, responsible for catalytic activity[1]. PARPs contain other functional units serving DNA or RNA binding (e.g. zinc fingers), signals that define their cellular localization (e.g. nuclear localization signal) or domains that enable protein-protein interaction, auto-poly(ADP-ribosyl)ation (PARylation) and interaction with ADP-ribose (ADPR) mono and polymers [1].

PARP-1, the first described PARP enzyme, is able to PARylate proteins. On the course of the reaction NAD⁺ is hydrolyzed into ADPR and nicotinamide. ADPR is then joined to glutamate, aspartate and lysine residues of acceptor proteins that is termed initiation and is followed by elongation or branching steps [2]. PAR has a short half-life due to rapid and efficient degradation by poly(ADP-ribose) glycohydrolase (PARG), ADP-ribosyl-acceptor hydrolase 3 (ARH3), ADP-ribosyl lyase and macrodomain containing proteins to ADPR[3]. ADPR is further degraded by nucleoside diphosphate linked to X (NUDIX) pyrophosphatases to ADP[4]. The major PAR-containing cellular compartment is the nucleus and to a lower extent the cytosol, while the presence of PAR in the mitochondria remains a debated issue [5, 6]. About 85-90% of PARP activity is related to PARP-1 while PARP-2 contributes to about 10-15% [7], only the remaining minority is covered by other members of the family. It should be noted also that mono or oligo-ADP-ribose on target proteins can be further elongated by PARylating PARPs[8]. There are several PARP inhibitors (PARPi's) in use for the blockade of PARPs, one of them, olaparib (AZD-2281, Lynparza) is now in clinical use. Most of these inhibitors are not isoform selective[9]. It is of note that there are natural inhibitors of PARPs such as niacin (vitamin B3) that is cleaved off NAD⁺ upon PARP activation or may stem from external source or fully external ones, like flavones, caffeine or theobromine [2, 10-12].

PARPs are best known for their activation upon DNA damage, however only PARP-1, PARP-2 and PARP-3 are DNA damage-dependent [13]. Besides DNA damage, PARPs are regulated through a wide array of posttranslational modifications such as ubiquitination, phosphorylation or acetylation, interaction with protein cofactors and through the modulation of their expression via miRNAs (PARP-1 by miRNA223; PARP-2 by miRNA149)[3, 14, 15]. It is a current endeavor to identify the methodology for the assessment of the PARylated proteins (the PARylome) with high throughput methods [16-18], however, there are already several hundreds of proteins identified in the 50 years history of PARylation (see the public database at ADPribоДB.leunglab.org).

There are several tasks in the cells performed or regulated by PARPs, in the current review we will focus on their role in metabolic regulation. For all other functions we refer the readers to recent thorough reviews on the topic[3, 14, 15].

2. PARPs in the transcriptional regulation of metabolism

PARP enzymes are deeply involved in transcriptional regulation. The best characterized member, PARP-1, may modulate chromatin through regulating DNA methylation, chromatin marks and chromatin composition (e.g. exchange between H1 and PARP-1) [14]. Also, independently of its catalytic activities PARP-1 may act as a scaffolding protein and may be involved in the recruitment of other coregulatory enzymes [14]. Whether PARP activity is necessary to accomplish these regulatory tasks varies between the individual cases.

Another possibility for transcriptional regulation is the interaction between PARPs and transcription (co)factors. PARPs were shown to interact with numerous metabolic transcription factors. The available information on the interaction between PARPs and most of these transcription factors is limited to the validation of interaction and the identification of a few targets (e.g. nuclear respiratory factor (NRF)-1 and NRF-2 that interact with PARP-1)[5]. Below those interactions will be detailed where more information is available on the molecular mechanism.

2.1 Interactions between PARPs and Sirtuins

PARP-1, -2 and -7 were shown to interact with sirtuins[2]. Sirtuins (SIRT1-7) are NAD⁺-dependent protein deacetylase enzymes with widespread metabolic and anti-aging properties. Sirtuins can deacetylate (frequently deacetylate) target proteins at the expense of cleaving an NAD⁺ molecule that is a common biochemical feature with PARPs [2]. The seven members of the sirtuin family can be found in all compartments of cells, generally nuclear (SIRT1, SIRT6, SIRT7), cytosolic (SIRT1, SIRT2) and mitochondrial (SIRT3, SIRT4, SIRT5) sirtuins are distinguished. The acyl group is coupled to ADP-ribose creating O-acyl-ADP-ribose. SIRT4 and SIRT6 were shown to exert NAD⁺-dependent mono-ADP-ribosyltransferase activity[2]. Sirtuins preferentially act as transcriptional cofactors[2].

There are several levels of the interaction between PARPs and sirtuins. First, those PARP and sirtuin enzymes that are present in the same compartment may compete for the common NAD⁺ substrate. PARP-1 binds and cleaves NAD⁺ more readily than SIRT1 (K_M PARP-1< K_M SIRT1, V_{max} PARP-1> V_{max} SIRT1), while the substrate binding and cleaving properties of PARP-2 and SIRT1 fall into the same range (K_M PARP-2~ K_M SIRT1, V_{max} PARP-2~ V_{max} SIRT1)[2]. In other words, when PARP-1 is activated it can easily outcompete SIRT1 for the common substrate. Since PARP-1 is activated in all cells to a certain extent, the deletion of PARP-1 induces NAD⁺ levels that in turn may switch on SIRT1. Importantly, the deletion of PARP-1

does not affect the activity of cytoplasmic SIRT2 or mitochondrial SIRT3 suggesting compartment-specific effects of PARP-1 deletion[2]. The application of PARP inhibitors phenocopy PARP-1 deletion[2]. Interestingly, tankyrase activity depends on cellular NAD⁺ production, a phenomenon yet without *physiological* roles [19].

Posttranslational modifications represent another level of interaction. PARP-1 is an acetylated protein that is active when acetylated [20]. Rajamohan and colleagues [20] showed that pharmacological activation of SIRT1 leads to the deacetylation and inhibition of PARP-1. Yet no studies have shown that PARP-1 could PARylate SIRT1 and hence modulate SIRT1 activity.

Activation of SIRT1 upon the deletion of PARP-1 is characteristic for the brown adipose tissue and skeletal muscle and leads to mitochondrial biogenesis[2].

The deletion of PARP-2 also leads to increases in SIRT1 activity. It was likely that the deletion of PARP-2 could also increase NAD⁺ levels, similarly to the deletion of PARP-1. However, in our study [21] NAD⁺ did not increase equivocally in all models calling for an alternative route. We found that PARP-2 acts as a repressor of SIRT1 expression and concluded that decreases in the expression of PARP-2 enhance SIRT1 expression and activity. This hypothesis has been challenged by a study [22] showing that transient SIRT1 overexpression does not enhance mitochondrial biogenesis. In fact, a third study by Mohamed and colleagues [23] showed consistent increases in NAD⁺ upon PARP-2 ablation making it more likely that PARP-2 and SIRT1 can be also interconnected through changes in NAD⁺ levels on the top of the regulation of SIRT1 expression. PARP-1 does not affect the expression of SIRT1[2, 24]. Activation of SIRT1 upon the deletion of PARP-2 is characteristic for the liver and skeletal muscle and leads to mitochondrial biogenesis in these tissues[2].

Typical targets of SIRT1 comprise transcription factors such as PGC-1α, FOXO1 or p53 that are activated upon deacetylation and clutch gene expression programs culminating in mitochondrial biogenesis [2]. It should be noted that the physiological effects of the PARP-sirtuin interaction is not limited to metabolic implications but (among others) cardiovascular and neurological pathologies are also mediated in that pathway (for review see [2]).

2.2 Interactions between PARPs and nuclear receptors

Nuclear receptors (NR) are transcription factors that are usually activated by lipophilic ligands [25]. NRs regulate an immense number of metabolic processes, as several hormone and metabolite receptors can be found among NRs. NRs work in dimers and require the presence of interacting proteins that form a complex over the NR and the neighboring chromatin. The composition of that complex changes as a function of the ligand binding of the NR changing between an activated state and a repressed state. Proteins that facilitate

NR activation are called co-activators, while those bringing about NR repression are called co-repressors; nevertheless, there are constitutive protein members of the complex too.

PARP-1, -2 and -7 enzymes had been shown to be involved in NR regulation (**Table 1**). PARP-1 is known to functionally and physically interact with both homodimeric (estrogen receptor (ER), progesterone receptor (PR)) and heterodimeric/orphan nuclear receptors (retinoic acid receptor (RAR), retinoic X receptor (RXR), thyroid hormone receptor (TR), peroxisome proliferators activated receptor family (PPARs), NR4A family (NOR1, Nurr1, Nurr7))[5]. PARP-1 predominantly binds to nuclear receptors through the second zinc finger of the DNA binding domain, however, direct binding of PARPs to DNA seems to be also important for the NR – PARP interaction[5].

In the case of the RXR/TR [26], liver X receptor (LXR) [27] and NOR-1 [28] PARP-1 activation has been reported to repress transcriptional activity. In contrast to that, activation through PARPs is also possible, PARP-7 can mono-ADP-ribosylate and activate LXR, while upon ER α activation PARP-1 is necessary for the recruitment of topoisomerase II β [29]. The role of PARP-1 in PPAR activation is inconsistent, PARP-1 overactivation can abrogate PPAR γ activity [30], while other studies showed that in the absence of PARP-1 PPAR γ activity is reduced [31, 32].

2.3 Interactions between PARP-2 and sterol-regulated element binding proteins (SREBPs)

Sterol-regulated element binding proteins SREBP-1 and SREBP-2 are cholesterol-sensitive transcription factors responsible for cholesterol and fatty acid (FA) import and synthesis [33, 34]. SREBP-1 and –2 reside in the Golgi apparatus until cellular cholesterol levels drop that activates proteases that can process SREBPs. Upon activation the membrane-bound SREBPs undergo multiple proteolytic cleavage. The resulting processed, active SREBPs translocate to the nucleus, where they bind to promoters of HMGCS, HMGCR, LDLR, FDPS, cytochrome P450, cyp51A1, SCD, ACACA, FASN, ACLY, PPAR γ and ME2 [33, 34]. The protein products of these genes induce cholesterol and FA biosynthesis. PARP-2 is a suppressor of the promoter of SREBP-1 through directly binding to promoter DNA, therefore the ablation of PARP-2 induces SREBP1 mRNA and protein expression[35]. Furthermore, in PARP-2 silenced hepatocytes the ratio between nuclear SREBP1/cytosolic SREBP1 increases through an unknown mechanism further enhancing SREBP1-mediated transcription [35].

2.4 Interaction of PARPs with other metabolic transcription factors

Although less characterized in terms of physiological outcomes, PARP-1 was shown to interact with other metabolic transcription factors, such as NRF-1, hypoxia-inducible factor

(HIF)-1 and -2 and p53. PARP-1 is necessary for the hypoxia-inducible factor (HIF)-1 mediated depression of mitochondrial complex II and IV and hence facilitates the down-regulation of mitochondrial activity. Interestingly, when PARPs are inhibited pharmacologically, HIF-1 activation is maintained longer, prolonging release from hypoxic accommodation [5]. Besides HIF-1, PARP-1 is a cofactor of HIF-2 and exert similar functions when in complex with HIF-1 [5]. PARP-1 is a positive cofactor of NRF-1, a transcriptional cofactor that, when activated, can enhance the transcription of, among others, PGC-1 α or PGC-1 β that are positive regulators of mitochondrial activity[5]. PARP-1 mediated activation of NRF-1 can be vital upon return from PARP-1 mediated depression of mitochondrial oxidation [5].

3 Relationship of PARPs and energy sensor systems

Cellular and organismal metabolism is regulated by a set of signal transduction pathways that translate environmental stimuli into metabolic responses. PARPs were shown to interfere with phosphatidylinositol 3-kinase (PI3K)–Akt–glycogen synthase kinase-3 (GSK3) and AMP activated kinase (AMPK) pathways [36, 37].

The activation of the PI3K – Akt pathway support mitochondrial activity and prevents mitochondrial transition pore opening, furthermore that pathway has pivotal role in the signal transduction events following the activation of certain tyrosine kinases such as the insulin receptor. The application of PARP inhibitors increased the activity of PI3K and Akt [36, 38]. Tankyrases (PARP-5a, PARP-5b) were also shown to regulate GSK3 and the PI3K[15].

AMPK is an energy sensor of cells that is activated by low ATP and high AMP levels (i.e. high AMP/ATP ratio). AMPK activation increases upon PARP-1 activation [39]. AMPK can phosphorylate and activate PARP-1 [37, 40]. AMPK and PARP-1 can mutually activate each other bringing about a feed forward loop. Furthermore, PARP-1 was shown to interact with the mechanistic target of rapamycin (mTOR) upon autophagy[41]. The activity of AMPK and mTOR is inversely related [42]. However, it remains an open question what is the relationship between the activation of mTOR AMPK and PARP-1.

4 Interplay of PARPs with mitochondrial homeostasis

The first observation in conjunction with PARPs and mitochondria was the devastating effects of PARP-1 overactivation upon excessive DNA damage on mitochondrial oxidative metabolism [43]. It is characterized by the loss of mitochondrial membrane potential, reduced activity of mitochondrial complex I, reduced mitochondrial oxidation and ATP production, superoxide production and the destruction of mitochondrial architecture[5]. PARP-1 activation opens mitochondrial transition pores (MTPs) promoting the release of mitochondrial content [43]. When MTPs are open cytochrome c, caspases and apoptosis

inducing factor (AIF) can leave the mitochondria [15, 44]. Later studies have shown that PARP activation impairs mitochondrial quality control as well, such as the mitochondrial unfolded protein response [45] and mitophagy [46]. Apparently, PARP-2 also participates in these processes, as the deletion of PARP-2 enhances mitochondrial activity [21, 23, 47].

At the molecular level several parallel pathways culminate in mitochondrial dysfunction upon PARP-1 overactivation. Berger and colleagues [48] suggested that cellular NAD⁺ levels are largely consumed upon PARP overactivation and consequently, NAD⁺ resynthesis depletes cellular energy reserves that then forces cells into a metabolic collapse. In addition to that, several mitotropic transcription factors are inhibited upon PARP activation (e.g. Sirt1), HIF is stabilized and the PI3K-Akt pathway is inhibited that suppress mitochondrial oxidative function on the long run. It should be also noted that PARP overactivation equally slows down glycolytic flux as well [5].

PAR molecules that are cleaved off from PARylated proteins and transported into the cytosol can also hamper mitochondrial oxidation. PAR can bind to the mitochondrial membrane declutching MTP opening[49] and can dissociate hexokinase from the mitochondrial surface uncoupling glycolysis and mitochondrial energy production [50]. Furthermore, degradation of PAR by NUDIX pyrophosphates[5] yields AMP and can be transported into the cytosol. AMP then can block adenine nucleotide translocase (ANT) in the mitochondrial membrane slowing down mitochondrial energy production[5]. Mitochondrial uncoupling leads to oxidative stress[43] that may have secondary inhibitory effects on mitochondrial enzymes [51].

A highly debated issue in the PARP field is the existence of an intrinsic PARP activity in the mitochondria. High NAD⁺ levels and enzymes for PAR degradation undoubtedly exist in the mitochondria, however, yet the presence of PARP activity is doubtful[5]. A recent study involving proximity ligation assays have provided evidence for the mitochondrial presence of PARP-1 and PAR and suggest a different timing for mitochondrial PARP-1 activation as compared to nuclear PARP-1 activation upon genotoxic stress[52]. For an in-depth review on the pros and cons of mitochondrial PARylation we refer the reader to a recent review [6].

PARP-mediated mitochondrial damage can serve as a trigger for cell death programs. It seems clear that PARP overactivation through depleting cellular energy stores makes it impossible to execute energy intensive cell death pathways such as the classical caspase-mediated apoptosis, but declutches necrosis or necroptosis[15]. In fact, during apoptosis PARP-1, PARP-2 and PARG are cleaved by caspases presumably to save energy to complete apoptosis and in line with that, PARP inhibition can convert necrotic processes into apoptosis as demonstrated on a large set of models[15]. Fatokun et al [53]have defined a PARylation-dependent mode of cell death characterized by enhanced nuclear PARylation, AIF translocation to the nucleus and the lack of caspase activation, coined parthanatos.

Genetic or pharmacological PARP inhibition can enhance mitochondrial energy production in contrast to PARP overactivation. Not only are the above deleterious processes reversed by PARP inhibition but pathways kick off that actively enhance mitochondrial oxidative metabolism such as AMPK activation by the AMP derived from PAR[5], activation of SIRT1[5], the activation of the PI3K-Akt [36] pathway or the improvement of mitochondrial unfolded protein response[45].

5 PARPs in higher order metabolic regulation

5.1 Regulatory role of PARPs in lipid metabolism

Despite the lack of comprehensive studies, our current knowledge strongly suggests that PARPs are intricately involved in lipid metabolism – it is noteworthy, that a hypothesis free *in silico* study clearly links PARP-2 to lipid metabolism [54].

Deletion or inhibition of PARP-1 or PARP-2 impacts on lipid storage. In the white adipose tissue (WAT), the role of PARP-1 in triglyceride storage seems to be complex and has debated points. In cellular models the absence or silencing of PARP-1 leads to lower lipid storage in the WAT through modulating PPAR γ transactivation [55, 56]. Most *in vivo* studies on PARPi-treated or PARP-1 knockout mice show, similarly to cellular studies, proportionally reduced WAT mass in PARPi-treated or PARP-1 $^{-/-}$ mice [24, 32, 57], however, another study by Devalaraja-Narashimha and Padanilam (2010) [58] showed an inverse behavior of PARP-1 $^{-/-}$ mice, namely PARP-1 knockout mice are more prone for obesity upon high fat feeding. PARP-2 through modulating PPAR γ activity facilitates lipid deposition in the WAT[15]. Triglycerides can be deposited in the liver as well. The deletion of PARP-2 protects against hepatic lipid deposition[15], similarly to PARP-1[59, 60].

Besides FA and triglyceride(TG) metabolism PARP-1 and PARP-2 influence cholesterol metabolism too. PARP-1 was shown to repress cholesterol efflux from macrophages through repressing LXR that diminishes the expression of ATP-binding cassette sub-family A Member 1 (ABCA1) a key cholesterol export protein [27]. In hepatocytes PARP-1 together with histone H1.2 is necessary for the efficient transcription of microsomal epoxide hydrolase (EPHX1), therefore PARP-1 may have role in facilitating bile acid export from hepatocytes[61]. PARP-2 was shown to repress hepatic cholesterol synthesis by repressing SREBP-1 expression [35]. The ablation of PARP-2, similarly to PARP-1, also led to decreased ABCA1 mRNA and protein expression and hepatic cholesterol accumulation [35] that is not due to changes in ABCA1 promoter activity [35]. It is likely that other PARPs (will be identified to influence lipid metabolism through pathways like Tyrosine Kinase Non Receptor 1 (TNK1) or LXR.

It should be noted that PARP activation and its deleterious effects seems to play important role in lipotoxicity. A toxic derivative of cholesterol, 7-ketocholesterol[62] can

activate PARP-1. Furthermore, FA-induced lipotoxicity also involves the NAD⁺- PARP-1 in hepatocytes [63]. In fact, Chen and colleagues[64] have identified ACBD3-ERK pathway to kick off PARP-1 activation as a result of FA treatment. Interestingly, α-lipoic acid can downregulate PARP-2 expression and hence exert a protective phenotype [65]. It is clear that the link between lipotoxicity and PARP activation is not elucidated in detail.

5.2PARPs and circadian rhythm, food uptake and hormonal control

5.2.1. Role of PARPs in circadian rhythm control

Systemic metabolism must be able to accommodate diurnal changes (e.g. feeding cycle, sleeping, etc.). The molecular basis of the diurnal cycling is the cyclic transcription, translation and degradation of four proteins Clock, Bmal, Per and Cry over a 24 hour cycle that impacts on systemic metabolism. Although this oscillation has its own cycle (~24 hours) in the body, external stimuli (e.g. feeding, changes in lighting) or internal stimuli (e.g. changes in serum nutrient concentrations) are capable of resetting our circadian clock. The central coordinator of human diurnal rhythm oscillations is the (ventromedial) hypothalamus [66]. The ventromedial hypothalamus senses nutrients in the circulation and in the cerebrospinal fluid, furthermore receives information from other cortical regions (e.g. from vision). These inputs are processed and converted into vegetative outputs (e.g. hunger/satiety) or into hormonal signals.

PARPs can regulate central and peripheral circadian responses. Several studies suggest that PARP-1 influences food uptake and feeding behavior [24, 58]. The deletion of PARP-1 in mice resulted in increased food uptake and altered circadian entrainment of the feeding behavior suggesting an impairment of the central (hypothalamic) circadian system. Importantly, feeding or fasting has been shown to impact on PARP-1 activity[24]. Conversely, deletion of PARP-2 does not alter food intake or feeding behavior [24].

There seems to be peripheral roles for PARP-1 in diurnal regulation. Asher and co-workers [67] described that in mouse liver PARP-1 activity follows circadian rhythm and is regulated by feeding providing an important link between the peripheral circadian rhythm and metabolism. PARP-1 can interact with circadian proteins, PARylate CLOCK which attenuates the interaction with PER and CRY protein. Thereby, PARP-1 alters the expression of several circadian genes [67].

5.2.2. PARPs in the regulation of glucose homeostasis

PARP-1, PARP-2, tankyrases (PARP-5a, PARP-5b) and PARP-16 have control over the intricate web of the hormonal regulation of glucose homeostasis through improving beta cell function or by regulating insulin sensitivity (**Fig. 1.**).

Pancreatic beta cells produce insulin that is the major hormone to eliminate glucose from the circulation. PARP-1 overactivation has major role in toxic beta cell death and PARP inhibition has protective role under these circumstances[15], moreover, PARP inhibition can even restore the function of the insulin promoter [68]. PARP-16 was shown to protect cells against ER stress, a major cause of beta cell dysfunction and beta cell death [69]. Interestingly, PARP-2 is required for beta cell function, its loss blunts beta cell proliferation probably through blocking pdx-1 expression[15]. Tankyrase 1 (PARP5a) is also involved in beta cell proliferation, its loss induces insulin secretion and beta cell proliferation[70]. It is also of note that PARP-1 interferes with GLP-1 signaling[71], an early signal that potentiates feeding-induced insulin secretion mTOR may represent additional pathways regulating beta cell function.

Insulin action is also under the control of PARPs. Deletion of PARP-1 or PARP-2 improves insulin sensitivity, similarly to short term PARP inhibition[15]. Improved insulin sensitivity is most probably attributed to glucose uptake into skeletal muscle driven by improved mitochondrial oxidation and isotype switch declutched by SIRT1 activation[15]. Tankyrase 1 and 2 (PARP5a, PARP5b) were shown to be involved in the insulin-induced Glut4 vesicle translocation in adipocytes[70].

5.2.3. PARPs and other metabolic hormones

Interplay between PARPs and other hormonal signaling systems were also described. Castration and lower androgen levels decrease PARP activity in neuronal ischemia-reperfusion injury[72]. Estradiol induces the expression of PARP-1 in the uterus [73]. These data implicate a correlation between estrogen signaling and PARP, and suggest that androgens or the androgen-to-estrogen ratios may be important for PARP activation. Finally, the inhibition of insulin-like growth factor (IGF)-1 signaling that induces cell death is potentiated by pharmacological PARP inhibition suggesting an interplay between the two systems[74].

6 PARP-mediated metabolic diseases

PARPs are implicated in a plethora of metabolic or metabolism-related pathologies (**Table 2.**). It is of note that these diseases are not purely metabolic pathologies, but have other features as well, such as metaflammation(low grade inflammation in metabolic pathologies such as in obesity) or cell death (for example in type I. diabetes). PARP-1 and PARP-2 are considered pro-inflammatory in Th1 and Th2-regulated pathologies[15], moreover, PARP inhibitors can blunt inflammation in humans [75] and metaflammation in mice [32]; PARP-mediated cell death was discussed earlier.

Tumors are characterized by metabolic rearrangements that is called Warburg metabolism (a name taken from Otto Warburg first describing cancer-related metabolic changes). A hallmark of Warburg metabolism is the suppression of mitochondrial oxidation, while pathways that improve mitochondrial oxidative metabolism counteract the Warburg rearrangement of metabolism[76]. It is of note that PARP overactivation can decrease mitochondrial activity that is a pro-Warburg, while genetic or pharmacological PARP inhibition increases oxidative metabolism that is an anti-Warburg feature.

Aging is a time-dependent functional decline characterized by numerous hallmarks (for review see [77]. Among the hallmarks metabolic decline is a major feature. Several studies have shown that PARP-1 activity increases on the course of aging (presumably due to the accumulating DNA damage) that decreases NAD⁺ content and consequently SIRT1 activity and mitochondrial biogenesis in metabolic tissues [78, 79]. In line with that, a mouse strain overexpressing an extra copy of human PARP-1 are protected against certain malignancies, while the incidence of age-related metabolic diseases (obesity, glucose intolerance) that is associated with mitochondrial dysfunction [80]. Not only insulin resistance of skeletal muscle, but the skeletal muscle fatigue is also related to dysregulation of SIRT1 by age-related PARP-1 activation [81]. Counteracting PARylation in skeletal muscle can be used to counteract muscle degeneration [82].

7 Conclusions

Our vision of how PARPs integrate metabolism has greatly enlarged in the past few years. Although it is easy to appreciate PARP-1 and PARP-2 as enzymes integrating environmental stress into metabolic circuits and hence damaging those processes, it seems that this cannot be taken as a general rule. PARP-1 and PARP-2 has positive metabolic properties and minor PARP isoforms also possess beneficial metabolic features. Key metabolic targets of PARPs are identified such as sirtuins, mitochondria, beta cells or skeletal muscle, There are apparent blurry points that warrant further research (e.g. PARP-mediated signaling pathways, metabolic diseases). A better understanding of cell/tissue or disease specificity of the PARP-mediated pathways will be needed. Studies on metabolome changes upon PARP activation/inhibition are arriving pointing towards biomarker identification [83, 84]. It seems there is much more to be found at the PARP – metabolism interface.

Conflict of interest

The authors declare no conflict of interest in relation with the present review.

Acknowledgment

We apologize to those whose works were not cited due to space restrictions.

Our work was supported by grants from NKFIH (K108308), the Momentum fellowship of the Hungarian Academy of Sciences and the University of Debrecen and the GINOP-2.3.2-15-2016-00006 project. The project is co-financed by the European Union and the European Regional Development Fund.

References

- [1] M.O. Hottiger, P.O. Hassa, B. Luscher, H. Schuler, F. Koch-Nolte, Toward a unified nomenclature for mammalian ADP-ribosyltransferases, *Trends Biochem Sci* 35(4) (2010) 208-19.
- [2] C. Canto, A.A. Sauve, P. Bai, Crosstalk between poly(ADP-ribose) polymerase and sirtuin enzymes, *Molecular aspects of medicine* 34(6) (2013) 1168-201.
- [3] M.O. Hottiger, Poly(ADP-ribose) polymerase inhibitor therapeutic effect: are we just scratching the surface?, *Expert Opin Ther Targets* 19(9) (2015) 1149-52. doi: 10.1517/14728222.2015.1073262. Epub 2015 Jul 27.
- [4] L. Formentini, A. Macchiarulo, G. Cipriani, E. Camaioli, E. Rapizzi, R. Pellicciari, F. Moroni, A. Chiarugi, Poly(ADP-ribose) catabolism triggers AMP-dependent mitochondrial energy failure, *J Biol Chem* 284(26) (2009) 17668-76.
- [5] P. Bai, L. Nagy, T. Fodor, L. Liaudet, P. Pacher, Poly(ADP-ribose) polymerases as modulators of mitochondrial activity, *Trends Endocrinol Metab* 26(2) (2015) 75-83.
- [6] A. Brunyanszki, B. Szczesny, L. Virág, C. Szabo, Mitochondrial poly(ADP-ribose) polymerase: The Wizard of Oz at work, *Free radical biology & medicine* (2016).
- [7] V. Schreiber, J.C. Ame, P. Dolle, I. Schultz, B. Rinaldi, V. Fraulob, J. Menissier-de Murcia, G. de Murcia, Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1, *The Journal of biological chemistry* 277(25) (2002) 23028-36.
- [8] A. Leung, T. Todorova, Y. Ando, P. Chang, Poly(ADP-ribose) regulates post-transcriptional gene regulation in the cytoplasm, *RNA biology* 9(5) (2012) 542-8.
- [9] N. Curtin, C. Szabo, Therapeutic Applications of PARP Inhibitors: Anticancer Therapy and Beyond, *Mol Aspects Med* 6 (2013) 1043-1258.
- [10] L. Geraets, H.J. Moonen, K. Brauers, E.F. Wouters, A. Bast, G.J. Hageman, Dietary flavones and flavonoles are inhibitors of poly(ADP-ribose)polymerase-1 in pulmonary epithelial cells, *J Nutr* 137(10) (2007) 2190-5.
- [11] L. Geraets, H.J. Moonen, E.F. Wouters, A. Bast, G.J. Hageman, Caffeine metabolites are inhibitors of the nuclear enzyme poly(ADP-ribose)polymerase-1 at physiological concentrations, *Biochem Pharmacol* 72(7) (2006) 902-10.
- [12] H.J. Moonen, L. Geraets, A. Vaarhorst, A. Bast, E.F. Wouters, G.J. Hageman, Theophylline prevents NAD⁺ depletion via PARP-1 inhibition in human pulmonary epithelial cells, *Biochem Biophys Res Commun* 338(4) (2005) 1805-10.
- [13] M. De Vos, V. Schreiber, F. Dantzer, The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art, *Biochem Pharmacol* 84(2) (2012) 137-46.
- [14] K.W. Ryu, D.S. Kim, W.L. Kraus, New facets in the regulation of gene expression by ADP-ribosylation and poly(ADP-ribose) polymerases, *Chemical reviews* 115(6) (2015) 2453-81.
- [15] P. Bai, Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance, *Mol Cell* 58(6) (2015) 947-958.
- [16] G. Bartolomei, M. Leutert, M. Manzo, T. Baubec, M.O. Hottiger, Analysis of Chromatin ADP-Ribosylation at the Genome-wide Level and at Specific Loci by ADPr-ChAP, *Molecular cell* 61(3) (2016) 474-85.
- [17] M. Isabelle, X. Moreel, J.P. Gagne, M. Rouleau, C. Ethier, P. Gagne, M.J. Hendzel, G.G. Poirier, Investigation of PARP-1, PARP-2, and PARG interactomes by affinity-purification mass spectrometry, *Proteome science* 8 (2010) 22.
- [18] B.A. Gibson, Y. Zhang, H. Jiang, K.M. Hussey, J.H. Shrimp, H. Lin, F. Schwede, Y. Yu, W.L. Kraus, Chemical genetic discovery of PARP targets reveals a role for PARP-1 in transcription elongation, *Science (New York, N.Y.)* (2016).
- [19] L. Zhong, T.Y. Yeh, J. Hao, N. Pourtabatabaei, S.K. Mahata, J. Shao, S.D. Chessler, N.W. Chi, Nutritional Energy Stimulates NAD⁺ Production to Promote Tankyrase-Mediated PARsylation in Insulinoma Cells, *PLoS One* 10(4) (2015) e0122948.

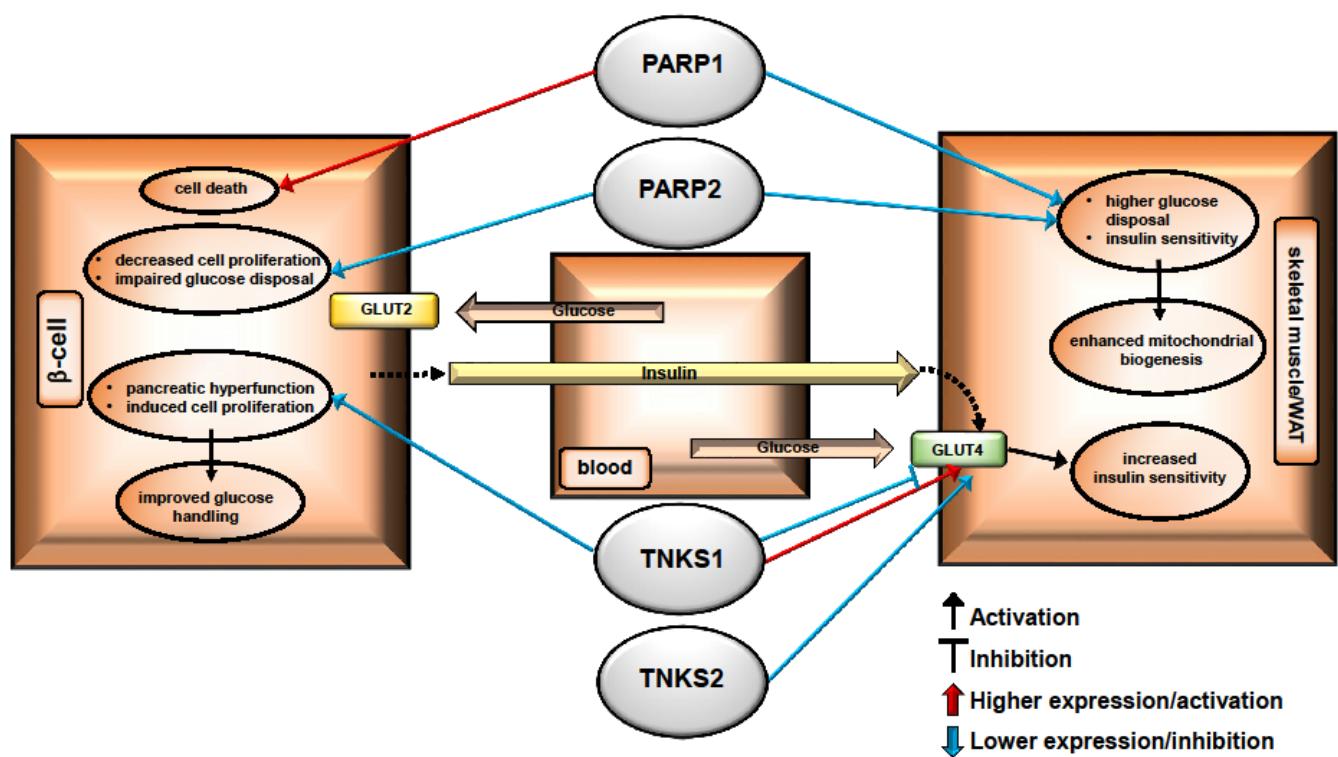
- [20] S.B. Rajamohan, V.B. Pillai, M. Gupta, N.R. Sundaresan, K.G. Birukov, S. Samant, M.O. Hottiger, M.P. Gupta, SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1, *Molecular and cellular biology* 29(15) (2009) 4116-29.
- [21] P. Bai, C. Canto, A. Brunyanszki, A. Huber, M. Szanto, Y. Cen, H. Yamamoto, S.M. Houten, B. Kiss, H. Oudart, P. Gergely, J. Menissier-de Murcia, V. Schreiber, A.A. Sauve, J. Auwerx, PARP-2 Regulates SIRT1 Expression and Whole-Body Energy Expenditure, *Cell Metab* 13(4) (2011) 450-60.
- [22] M. Boutant, S.S. Kulkarni, M. Joffraud, F. Raymond, S. Metairon, P. Descombes, C. Canto, SIRT1 Gain of Function Does Not Mimic or Enhance the Adaptations to Intermittent Fasting, *Cell reports* 14(9) (2016) 2068-75.
- [23] J.S. Mohamed, A. Hajira, P.S. Pardo, A.M. Boriek, MicroRNA-149 Inhibits PARP-2 and Promotes Mitochondrial Biogenesis via SIRT-1/PGC-1alpha Network in Skeletal Muscle, *Diabetes* 63(5) (2014) 1546-59.
- [24] P. Bai, C. Canto, H. Oudart, A. Brunyanszki, Y. Cen, C. Thomas, H. Yamamoto, A. Huber, B. Kiss, R.H. Houtkooper, K. Schoonjans, V. Schreiber, A.A. Sauve, J. Menissier-de Murcia, J. Auwerx, PARP-1 Inhibition Increases Mitochondrial Metabolism through SIRT1 Activation, *Cell Metab* 13(4) (2011) 461-8.
- [25] R.M. Evans, D.J. Mangelsdorf, Nuclear receptors, RXR, and the big bang, *Cell* 157(1) (2014) 255-266.
- [26] T. Miyamoto, T. Kakizawa, K. Hashizume, Inhibition of nuclear receptor signalling by poly(ADP-ribose) polymerase, *Molecular and cellular biology* 19(4) (1999) 2644-9.
- [27] E. Shrestha, M.A. Hussein, J.N. Savas, M. Ouimet, T.J. Barrett, S. Leone, J.R. Yates, 3rd, K.J. Moore, E.A. Fisher, M.J. Garabedian, Poly(ADP-ribose) Polymerase 1 Represses Liver X Receptor-mediated ABCA1 Expression and Cholesterol Efflux in Macrophages, *The Journal of biological chemistry* 291(21) (2016) 11172-84.
- [28] N. Ohkura, Y. Nagamura, T. Tsukada, Differential transactivation by orphan nuclear receptor NOR1 and its fusion gene product EWS/NOR1: possible involvement of poly(ADP-ribose) polymerase I, PARP-1, *Journal of cellular biochemistry* 105(3) (2008) 785-800.
- [29] B.G. Ju, M.G. Rosenfeld, A breaking strategy for topoisomerase IIbeta/PARP-1-dependent regulated transcription, *Cell cycle (Georgetown, Tex.)* 5(22) (2006) 2557-60.
- [30] D. Huang, C. Yang, Y. Wang, Y. Liao, K. Huang, PARP-1 suppresses adiponectin expression through poly(ADP-ribosylation) of PPAR gamma in cardiac fibroblasts, *Cardiovascular research* 81(1) (2009) 98-107.
- [31] S. Erener, M. Hesse, R. Kostadinova, M.O. Hottiger, Poly(ADP-Ribose)Polymerase-1 (PARP1) Controls Adipogenic Gene Expression and Adipocyte Function, *Mol Endocrinol* 26(1) (2012) 79-86.
- [32] M. Lehmann, E. Pirinen, A. Mirsaidi, F.A. Kunze, P.J. Richards, J. Auwerx, M.O. Hottiger, ARTD1-induced poly-ADP-ribose formation enhances PPARgamma ligand binding and co-factor exchange, *Nucleic Acids Res* 43(1) (2015) 129-42.
- [33] X. Wang, R. Sato, M.S. Brown, X. Hua, J.L. Goldstein, SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis, *Cell* 77(1) (1994) 53-62.
- [34] X. Hua, C. Yokoyama, J. Wu, M.R. Briggs, M.S. Brown, J.L. Goldstein, X. Wang, SREBP-2, a second basic-helix-loop-helix zipper protein that stimulates transcription by binding to a sterol regulatory element, *Proc Natl Acad Sci U S A* 90(24) (1993) 11603-7.
- [35] M. Szanto, A. Brunyanszki, J. Marton, G. Vamosi, L. Nagy, T. Fodor, B. Kiss, L. Virág, P. Gergely, P. Bai, Deletion of PARP-2 induces hepatic cholesterol accumulation and decrease in HDL levels, *Biochimica et biophysica acta* 1842(4) (2014) 594-602.
- [36] A. Tapodi, B. Debreceni, K. Hanto, Z. Bognar, I. Wittmann, F. Gallyas, Jr., G. Varbiro, B. Sumegi, 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(42) (2005) 35767-75.
- [37] J.W. Walker, H.B. Jijon, K.L. Madsen, AMP-activated protein kinase is a positive regulator of poly(ADP-ribose) polymerase, *Biochem Biophys Res Commun* 342(1) (2006) 336-41.

- [38] A. Szanto, E.E. Hellebrand, Z. Bognar, Z. Tucsek, A. Szabo, F. Gallyas, Jr., B. Sumegi, G. Varbiro, PARP-1 inhibition-induced activation of PI-3-kinase-Akt pathway promotes resistance to taxol, *Biochem Pharmacol* 77(8) (2009) 1348-57.
- [39] J. Zhou, S. Ng, Q. Huang, Y.T. Wu, Z. Li, S.Q. Yao, H.M. Shen, AMPK mediates a pro-survival autophagy downstream of PARP-1 activation in response to DNA alkylating agents, *FEBS Lett* 587(2) (2013) 170-7.
- [40] B. Gongol, T. Marin, I.C. Peng, B. Woo, M. Martin, S. King, W. Sun, D.A. Johnson, S. Chien, J.Y. Shyy, AMPKalpha2 exerts its anti-inflammatory effects through PARP-1 and Bcl-6, *Proc Natl Acad Sci U S A* 110(8) (2013) 3161-6.
- [41] J.M. Rodriguez-Vargas, M.J. Ruiz-Magana, C. Ruiz-Ruiz, J. Majuelos-Melguizo, A. Peralta-Leal, M.I. Rodriguez, J.A. Munoz-Gamez, M.R. de Almodovar, E. Siles, A.L. Rivas, M. Jaattela, F.J. Oliver, ROS-induced DNA damage and PARP-1 are required for optimal induction of starvation-induced autophagy, *Cell research* 22(7) (2012) 1181-98.
- [42] D.D. Sarbassov, S.M. Ali, D.M. Sabatini, Growing roles for the mTOR pathway, *Curr Opin Cell Biol* 17(6) (2005) 596-603.
- [43] L. Virág, A.L. Salzman, C. Szabo, Poly(ADP-ribose) synthetase activation mediates mitochondrial injury during oxidant-induced cell death, *Journal of immunology* (Baltimore, Md. : 1950) 161(7) (1998) 3753-9.
- [44] S.W. Yu, H. Wang, M.F. Poitras, C. Coombs, W.J. Bowers, H.J. Federoff, G.G. Poirier, T.M. Dawson, V.L. Dawson, Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor, *Science* (New York, N.Y.) 297(5579) (2002) 259-63.
- [45] E. Pirinen, C. Canto, Y.S. Jo, L. Morato, H. Zhang, K.J. Menzies, E.G. Williams, L. Mouchiroud, N. Moullan, C. Hagberg, W. Li, S. Timmers, R. Imhof, J. Verbeek, A. Pujol, B. van Loon, C. Visconti, M. Zeviani, P. Schrauwen, A.A. Sauve, K. Schoonjans, J. Auwerx, Pharmacological Inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle, *Cell metabolism* 19(6) (2014) 1034-41.
- [46] E.F. Fang, M. Scheibye-Knudsen, L.E. Brace, H. Kassahun, T. Sengupta, H. Nilsen, J.R. Mitchell, D.L. Croteau, V.A. Bohr, Defective Mitophagy in XPA via PARP-1 Hyperactivation and NAD(+)/SIRT1 Reduction, *Cell* 157(4) (2014) 882-96.
- [47] M. Szántó, I. Rutkai, C. Hegedus, A. Czikora, M. Rózsahegyi, B. Kiss, L. Virág, P. Gergely, A. Tóth, P. Bai, Poly(ADP-ribose) polymerase-2 depletion reduces doxorubicin-induced damage through SIRT1 induction, *Cardiovascular Research* 92(3) (2011) 430-438.
- [48] N.A. Berger, J.L. Sims, D.M. Catino, S.J. Berger, Poly(ADP-ribose) polymerase mediates the suicide response to massive DNA damage: studies in normal and DNA-repair defective cells, *Princess Takamatsu Symp* 13 (1983) 219-26.
- [49] Y. Wang, N.S. Kim, J.F. Haince, H.C. Kang, K.K. David, S.A. Andrabi, G.G. Poirier, V.L. Dawson, T.M. Dawson, Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos), *Science signaling* 4(167) (2011) ra20.
- [50] S.A. Andrabi, G.K. Umanah, C. Chang, D.A. Stevens, S.S. Karuppagounder, J.P. Gagne, G.G. Poirier, V.L. Dawson, T.M. Dawson, Poly(ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis, *Proc Natl Acad Sci U S A* 111(28) (2014) 10209-14.
- [51] S.J. Wei, J.H. Xing, B.L. Wang, L. Xue, J.L. Wang, R. Li, W.D. Qin, J. Wang, X.P. Wang, M.X. Zhang, Y.G. Chen, Poly(ADP-ribose) polymerase inhibition prevents reactive oxygen species induced inhibition of aldehyde dehydrogenase2 activity, *Biochim Biophys Acta* 1833(3) (2013) 479-86.
- [52] B. Szczesny, A. Brunyanszki, G. Olah, S. Mitra, C. Szabo, 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* 42(21) (2014) 13161-73.
- [53] A.A. Fatokun, V.L. Dawson, T.M. Dawson, Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities, *Br J Pharmacol* 171(8) (2014) 2000-16.
- [54] A. Manunza, J. Casellas, R. Quintanilla, R. Gonzalez-Prendes, R.N. Pena, J. Tibau, A. Mercade, A. Castello, N. Aznarez, J. Hernandez-Sanchez, M. Amills, A genome-wide association analysis for

porcine serum lipid traits reveals the existence of age-specific genetic determinants, BMC genomics 15 (2014) 758.

- [55] M.E. Smulson, V.H. Kang, J.M. Ntambi, D.S. Rosenthal, R. Ding, C.M. Simbulan, Requirement for the expression of poly(ADP-ribose) polymerase during the early stages of differentiation of 3T3-L1 preadipocytes, as studied by antisense RNA induction, The Journal of biological chemistry 270(1) (1995) 119-27.
- [56] S. Erener, A. Mirsaidi, M. Hesse, A.N. Tiaden, H. Ellingsgaard, R. Kostadinova, M.Y. Donath, P.J. Richards, M.O. Hottiger, ARTD1 deletion causes increased hepatic lipid accumulation in mice fed a high-fat diet and impairs adipocyte function and differentiation, Faseb J 26(6) (2012) 2631-2638.
- [57] R. Cerutti, E. Pirinen, C. Lamperti, S. Marchet, A.A. Sauve, W. Li, V. Leoni, E.A. Schon, F. Dantzer, J. Auwerx, C. Viscomi, M. Zeviani, NAD(+) -dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease, Cell metabolism 19(6) (2014) 1042-9.
- [58] K. Devalaraja-Narashimha, B.J. Padanilam, PARP1 deficiency exacerbates diet-induced obesity in mice, J Endocrinol 205(3) (2010) 243-52.
- [59] K. Gariani, D. Ryu, K.J. Menzies, H.S. Yi, S. Stein, H. Zhang, A. Perino, V. Lemos, E. Katsyuba, P. Jha, S. Vijgen, L. Rubbia-Brandt, Y.K. Kim, J.T. Kim, K.S. Kim, M. Shong, K. Schoonjans, J. Auwerx, Inhibiting poly ADP-ribosylation increases fatty acid oxidation and protects against fatty liver disease, J Hepatol 20(16) (2016) 30508-6.
- [60] P. Mukhopadhyay, B. Horváth, M. Rajesh, Z.V. Varga, K. Gariani, D. Ryu, Z. Cao, E. Holovac, O. Park, Z. Zhou, M.J. Xu, W. Wang, G. Godlewski, J. Paloczi, B.T. Nemeth, Y. Persidsky, L. Liaudet, G. Haskó, P. Bai, H.A. Boulares, J. Auwerx, B. Gao, P. Pacher, PARP inhibition protects against alcoholic and nonalcoholic steatohepatitis, Journal of Hepatology (2016) in press.
- [61] H. Peng, Q.S. Zhu, S. Zhong, D. Levy, Transcription of the Human Microsomal Epoxide Hydrolase Gene (EPHX1) Is Regulated by PARP-1 and Histone H1.2. Association with Sodium-Dependent Bile Acid Transport, PLoS One 10(5) (2015) e0125318.
- [62] A. Diestel, O. Aktas, D. Hackel, I. Hake, S. Meier, C.S. Raine, R. Nitsch, F. Zipp, O. Ullrich, Activation of microglial poly(ADP-ribose)-polymerase-1 by cholesterol breakdown products during neuroinflammation: a link between demyelination and neuronal damage, The Journal of experimental medicine 198(11) (2003) 1729-40.
- [63] J. Pang, J. Cui, H. Gong, C. Xi, T.M. Zhang, Effect of NAD on PARP-mediated insulin sensitivity in oleic acid treated hepatocytes, Journal of cellular physiology 230(7) (2015) 1607-13.
- [64] Y. Chen, S. Bang, S. Park, H. Shi, S.F. Kim, Acyl-CoA-binding domain containing 3 modulates NAD⁺ metabolism through activating poly(ADP-ribose) polymerase 1, The Biochemical journal 469(2) (2015) 189-98.
- [65] L. Zhang, J. Zou, E. Chai, Y. Qi, Y. Zhang, Alpha-lipoic acid attenuates cardiac hypertrophy via downregulation of PARP-2 and subsequent activation of SIRT-1, European journal of pharmacology 744 (2014) 203-10.
- [66] M.O. Dietrich, T.L. Horvath, Feeding signals and brain circuitry, The European journal of neuroscience 30(9) (2009) 1688-96.
- [67] G. Asher, H. Reinke, M. Altmeyer, M. Gutierrez-Arcelus, M.O. Hottiger, U. Schibler, Poly(ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding, Cell 142(6) (2010) 943-53.
- [68] D.Z. Ye, M.H. Tai, K.D. Linning, C. Szabo, L.K. Olson, MafA expression and insulin promoter activity are induced by nicotinamide and related compounds in INS-1 pancreatic beta-cells, Diabetes 55(3) (2006) 742-50.
- [69] M. Jwa, P. Chang, PARP16 is a tail-anchored endoplasmic reticulum protein required for the PERK- and IRE1alpha-mediated unfolded protein response, Nat Cell Biol 14(11) (2012) 1223-30.
- [70] T.Y. Yeh, K.K. Beiswenger, P. Li, K.E. Bolin, R.M. Lee, T.S. Tsao, A.N. Murphy, A.L. Hevener, N.W. Chi, Hypermetabolism, hyperphagia, and reduced adiposity in tankyrase-deficient mice, Diabetes 58(11) (2009) 2476-85.

- [71] F.Q. Liu, X.L. Zhang, L. Gong, X.P. Wang, J. Wang, X.G. Hou, Y. Sun, W.D. Qin, S.J. Wei, Y. Zhang, L. Chen, M.X. Zhang, Glucagon-like peptide 1 protects microvascular endothelial cells by inactivating the PARP-1/iNOS/NO pathway, *Mol Cell Endocrinol* 339(1-2) (2011) 25-33.
- [72] T. Shimizu, T.A. Macey, N. Quillinan, J. Klawitter, A.L. Perraud, R.J. Traystman, P.S. Herson, Androgen and PARP-1 regulation of TRPM2 channels after ischemic injury, *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 33(10) (2013) 1549-55.
- [73] A. Joshi, S. Mahfooz, V.K. Maurya, V. Kumar, C.S. Basanna, G. Kaur, K. Hanif, R.K. Jha, PARP1 during embryo implantation and its upregulation by oestradiol in mice, *Reproduction* 147(6) (2014) 765-80.
- [74] O. Amin, M.C. Beauchamp, P.A. Nader, I. Laskov, S. Iqbal, C.A. Philip, A. Yasmeen, W.H. Gotlieb, Suppression of Homologous Recombination by insulin-like growth factor-1 inhibition sensitizes cancer cells to PARP inhibitors, *BMC cancer* 15 (2015) 817.
- [75] D.A. Morrow, C.M. Brickman, S.A. Murphy, K. Baran, R. Krakover, H. Dauerman, S. Kumar, N. Slomowitz, L. Grip, C.H. McCabe, A.L. Salzman, A randomized, placebo-controlled trial to evaluate the tolerability, safety, pharmacokinetics, and pharmacodynamics of a potent inhibitor of poly(ADP-ribose) polymerase (INO-1001) in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of the TIMI 37 trial, *J Thromb Thrombolysis* 27(4) (2009) 359-64.
- [76] G. Kroemer, J. Pouyssegur, Tumor Cell Metabolism: Cancer's Achilles' Heel, *Cancer Cell* 13(6) (2008) 472-482.
- [77] C. Lopez-Otin, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging, *Cell* 153(6) (2013) 1194-217.
- [78] H. Massudi, R. Grant, N. Braidy, J. Guest, B. Farnsworth, G.J. Guillemin, Age-associated changes in oxidative stress and NAD⁺ metabolism in human tissue, *PloS one* 7(7) (2012) e42357.
- [79] N. Braidy, G.J. Guillemin, H. Mansour, T. Chan-Ling, A. Poljak, R. Grant, Age related changes in NAD⁺ metabolism oxidative stress and Sirt1 activity in wistar rats, *PLoS One* 6(4) (2011) e19194.
- [80] A. Mangerich, N. Herbach, B. Hanf, A. Fischbach, O. Popp, M. Moreno-Villanueva, O.T. Bruns, A. Burkle, Inflammatory and age-related pathologies in mice with ectopic expression of human PARP-1, *Mech Ageing Dev* 131(6) (2010) 389-404.
- [81] J.S. Mohamed, J.C. Wilson, M.J. Myers, K.J. Sisson, S.E. Alway, Dysregulation of SIRT-1 in aging mice increases skeletal muscle fatigue by a PARP-1-dependent mechanism, *Aging (Albany NY)* 6(10) (2014) 820-834.
- [82] D. Ryu, H. Zhang, E.R. Ropelle, V. Sorrentino, D.A. Mazala, L. Mouchiroud, P.L. Marshall, M.D. Campbell, A.S. Ali, G.M. Knowels, S. Bellemin, S.R. Iyer, X. Wang, K. Gariani, A.A. Sauve, C. Canto, K.E. Conley, L. Walter, R.M. Lovering, E.R. Chin, B.J. Jasmin, D.J. Marcinek, K.J. Menzies, J. Auwerx, NAD⁺ repletion improves muscle function in muscular dystrophy and counters global PARylation, *Sci Transl Med.* 8(361) (2016) 361ra139.
- [83] E.C. Laiakis, E.L. Pannkuk, M.E. Diaz-Rubio, Y.W. Wang, T.D. Mak, C.M. Simbulan-Rosenthal, D.J. Brenner, A.J. Fornace, Jr., Implications of genotypic differences in the generation of a urinary metabolomics radiation signature, *Mutation research* 788 (2016) 41-9.
- [84] A.R. Bianchi, C. Ferreri, S. Ruggiero, S. Deplano, V. Sunda, G. Galloro, C. Formisano, M.R. Faraone Mennella, Automodification of PARP and fatty acid-based membrane lipidome as a promising integrated biomarker panel in molecular medicine, *Biomarkers in medicine* 10(3) (2016) 229-42.

Figure caption**Figure 1. PARP-regulated pathways in beta cells and in peripheral insulin action.**

Tables**Table 1. Known PARP-interacting NRs**

Nuclear receptor	PARP partner	Effects
ER	PARP-1/2	PARP-1 is a positive regulator of ER. PARP-1 is required to reseal topoisomerase IIβ-induced DNA breaks associated with ER activation. Estrogen is capable of counteracting PARP activation with an unknown mechanism. PARP-2 does not interfere with ER β PARP-2 is a positive regulator of ER α
PR	PARP-1	Progesterone stimulates PARP-1. PR interacts with PARP-1.
RAR	PARP-1	PARP-1 is a positive cofactor of RAR.
TR	PARP-1	PARP-1 is a positive cofactor of TR. PARP-1 is necessary for the activity of TR/RXR heterodimer, while its overexpression hampers nuclear receptor transactivation.
RXR/PPAR α	PARP-1	PARP-1 PARylates and inactivates PPAR α
RXR/PPAR γ	PARP-1/2	PARP-2 is a positive cofactor of the RXR/PPAR γ heterodimer binding to PPAR γ -mediated promoters. The ablation of PARP-2 leads to WAT hypofunction. PARP-1 is necessary for normal expression of PPAR γ -mediated genes in adipocytes. PARP-1 overactivation hampers adiponectin expression by PARylating PPAR γ . PARP-1 inhibition results in reduced adipose tissue inflammation in obese mice. PARP-1 is required for PPAR γ cofactor exchange.
RXR	PARP-1	The second Zn finger of PARP-1 is the interaction surface between RXR and PARP-1.
NOR1, Nur1	PARP-1	PARP-1 is a cofactor of NOR-1 and Nur-1 transcription. PARP-1 overexpression represses NOR-1 and Nur-1 transcription.
AR	PARP-1	PARP-1 is a positive regulator of the AR promoter.
LXR	PARP-1 PARP-2 PARP-7	PARP-1 represses ABCA1 expression and cholesterol efflux in macrophages. PARP-2 is a positive cofactor of LXR PARP-7 coregulates (activates) LXR through ADP-ribosylation.

Table 2. PARP-mediated metabolic diseases

Disease / Condition	PARP(s) involved	Mechanism	Model / Source of evidence
Obesity	PARP-1, PARP-2	Down-regulation of NAD ⁺ /sirtuin pathway is related to obesity.	Monozygous twin study, PARP-1 knockout mice, PARP-2 knockout mice, PARPi
		Impaired PPAR γ activation upon PARP-1 or PARP-2 silencing	PARP-1 knockout mice, PARP-2 knockout mice, PARP-1 and PARP-2 silencing
Type I diabetes	Not specified	PARP inhibitors prevent diabetes by reducing β -cell apoptosis.	Diabetes-prone NOD mouse model, PARPi
Type II diabetes	PARP-1, PARP-2	Deletion, silencing or inhibition of PARP-1 or PARP-2 improves mitochondrial biogenesis and insulin sensitivity in the liver and skeletal muscle	PARP-1 knockout mice, PARP-2 knockout mice, PARP-1 and PARP-2 silencing in cellular models, PARPi studies
	Not specified	PARP activity correlates with OSA, DFU and lower IENFD .	Cross-sectional study of adults with type 2 diabetes
Diabetic sequels	PARP-1	PARP-1 deletion or PARPi treatment protect against diabetic (micro)vascular dysfunction	T2DM mouse model, Ex vivo model using mouse IMECs (MS-1 cells)
	not specified	PARP inhibition promotes wound healing and angiogenesis at ischemic wounds in diabetes	FVB/NJ mouse model
	PARP-1	PARP-1 inhibiting flavonoids attenuate LPS-induced cytokine release from leukocytes.	Male patients with T2D
	not specified	PARP inhibition ameliorates development of diabetic nephropathy.	type 2 diabetes db/db mouse model
	PARP-1	PARP-1 inhibition protect against diabetic oculopathy	murine type 2 diabetes models
AFLD	PARP -1	Alcohol mediated increase in PARP-1 activity and decrease in SIRT1 activity perturbs liver clock leading to the dysfunction of lipid metabolic pathways. PARP inhibition or the inactivation of the PARP-1 gene is anti-inflammatory in AFLD	Alcohol fed mouse model Alcohol fed mouse model
NAFLD	PARP-1	PARP -1 inhibition leads to increased mitochondrial metabolism through SIRT1 activation.	PARP-1 knockdown mouse model PARP-1 knockdown mouse model

		PPAR α PARylation suppresses hepatic fatty acid oxidation.	
Toxic steatohepatitis	PARP-7	Absence of PARP7 (TiPARP) results in increased AHR activity due to reduced mono-ADP-ribosylation leading to increased dioxin sensitivity.	PARP-7 $^{-/-}$ mouse model
PCOS	PARP-1	Negative correlation between PARP activity and PCOS related metabolic disorders	Wistar rat model
Atherosclerosis	PARP-1, PARP-2	PARP-1 represses LXR mediated ABCA1 expression. PARP-2 deletion correlates with lowered ABCA1 expression although the exact mechanism is unknown.	PARP-1 knockout mice, PARP-2 knockout mice
Hypercholesterolemia	PARP-2	In PARP-2 $^{-/-}$ mice serum HDL levels decrease while LDL levels remains unchanged.	PARP-2 knockout mice
Hyperlipidemia	PARP-1	Knockout of PARP-1 decreases serum TG and FFA levels.	PARP-1 knockout mice
Cancer cachexia	PARP-1, PARP-2	PARP-1 and PARP-2 deletion counterbalances downregulation of muscle-specific microRNAs ultimately leading to improvements in body and muscle weights of cachectic animals.	PARP-1 knockout mice, PARP-2 knockout mice
Hashimoto thyroiditis	PARP-1	Association only, speculated connection between PARP-1 variants and PARP-1 regulated inflammatory response gene expressions	Human patient study
Aging	PARP-1	Lower PARP-1 expression improves aging-related metabolic pathologies.	In vitro experiments, animal models and human studies