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Review

PARPs in lipid metabolism and related diseases

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ABSTRACT

PARPs and tankyrases (TNKS) represent a family of 17 proteins. PARPs and tankyrases were originally identified as DNA repair factors, nevertheless, recent advances have shed light on their role in lipid metabolism. To date, PARP1, PARP2, PARP3, tankyrases, PARP9, PARP10, PARP14 were reported to have multi-pronged connections to lipid metabolism. The activity of PARP enzymes is fine-tuned by a set of cholesterol-based compounds as oxidized cholesterol derivatives, steroid hormones or bile acids. In turn, PARPs modulate several key processes of lipid homeostasis (lipotoxicity, fatty acid and steroid biosynthesis, lipoprotein homeostasis, fatty acid oxidation, etc.). PARPs are also cofactors of lipid-responsive nuclear receptors and transcription factors through which PARPs regulate lipid metabolism and lipid homeostasis. PARP activation often represents a disruptive signal to (lipid) metabolism, and PARP-dependent changes to lipid metabolism have pathophysiological role in the development of hyperlipidemia, obesity, alcoholic and non-alcoholic fatty liver disease, type II diabetes and its

Abbreviations: ABCA1, ATP-binding cassette sub-family A Member 1; ACAT1, Mitochondrial acyl-coenzyme A/cholesterol acyltransferase-1; ACBD3, Acyl-CoA-binding domain containing 3; ADPR, ADP-ribose; AFLD, Alcoholic fatty liver disease; AHR, Aryl hydrocarbon receptor; ALDH2, Aldehyde dehydrogenase 2; AMPK, AMP-activated protein kinase; ApoB, Apolipoprotein B; AR, Androgen receptor; ARH3, ADP-ribosyl-acceptor hydrolase-3; ARTs, ADP-ribosyl transferases; ARTD, Diphtheria toxin-like ADP-Ribosyltransferases; C/EBPα, CCAAT-enhancer-binding protein alpha; cyp, Cytochrome P450; DGAT, Diacylglycerol O-acyltransferase; DHT, dihydrotestosterone; EBF, Early B cell factor; EMA, European Medicines Authority; eNOS, Endothelial nitrogen oxide synthase; EPHX1, Microsomal epoxide hydrolase; ERα, Estrogen receptor alpha; ERK, Extracellular signal-regulated kinase; FABP7, Fatty acid binding protein 7; FDA, Food and Drug Administration; FoxO1, Forkhead transcription factor O1; GATA, GATA-binding factor; *GLP-1*, Glucagon-like peptide-1; Glut4, Glucose transporter-4; GR, Glucocorticoid receptor; hADMSC, Human adipose tissue-derived mesenchymal stem cells; HCD, High cholesterol diet; HDAC, Histone deacetylase; HDL, High density lipoprotein; HFD, High-fat diet; HFRD, High fructose diet; HNF4, Hepatocyte nuclear factor 4; HPF1, Histone PARylation factor 1; Hsd17b11, Estradiol 17-beta-dehydrogenase 11; H2BE35, Histone H2B on glutamate 35; IDL, Intermediate density lipoprotein; IGF-1, Insulin-like growth factor-1; iNOS, Inducible nitrogen oxide synthase; InsR, Insulin receptor; iPSCs, Induced pluripotent stem cells; IRF, Interferon-regulatory factor; JNK, Jun kinase; KLF, Krüppel-like factor; LDL, Low density lipoprotein; LPS, Bacterial lipopolysaccharide; LXR, Liver X receptor; MARylation, Mono(ADP-ribosyl)ation; MCD, Methionine-choline deficient; mTORC1/2, Mammalian/mechanistic Target of Rapamycin Complex 1/2; NAD+, Oxidized nicotinamide adenine dinucleotide; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NCoR-1, Nuclear Receptor Corepressor 1; NEFA, Non-esterified fatty acids; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NMN, Nicotinamide mononucleotide; HIF, hypoxia inducible factor; NMNAT, Nicotinamide/nicotinic acid mononucleotide adenylyltransferase; *NOR1*, Neuron-derived orphan *receptor* 1; NOx, Nitrogen oxides; NR, Nuclear receptor; oxLDL, Oxidized LDL; OXPHOS, Oxidative phosphorylation; PAR, poly(ADP-ribose); PARG, Poly(ADP-ribose) glycohydrolase; PARPi, PARP inhibitor; PARylation, Poly(ADP-ribosyl)ation; PPARα, Peroxisome proliferator-activated receptor alpha; PPARγ, Peroxisome proliferator-activated receptor gamma; PR, Progesterone receptor; *P-Sel*, *P-selectin*; PTMs, Post-translational modifications; RXRα, Retinoid X-receptor alpha; SAHA, Suberoylanilide hydroxamic acid; snoRNAs, Short nucleolar RNAs; SNP, Single nucleotide polymorphism; Srd5a1, 5α-reductase; SREBP, Sterol regulatory-element binding protein; StAR, steroidogenic acute regulatory protein; STAT, Signal transducer and activator of transcription; TC, Total cholesterol; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TF, Transcription factors; TG, Serum triglyceride; TLR2, Toll-like receptor-2; *TNFα*, *Tumor necrosis factor α*; TNKS, Tankyrase; TRPM2, Transient receptor potential M2; UCP, Uncoupling protein; V-Cam, Vascular cell *adhesion* molecule 1 (*CD106)*; VLDL, Very low density lipoprotein; VPA, Valproic acid; WAT, White adipose tissue; WHO, World Health Organization; 7KC, 7-ketocholesterol; 15-HC, 15a-hydroxicholestene.

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PGC1α
nuclear receptor
lipotoxicity
atherosclerosis
PPARα
PPARγ
Estrogen receptor
C/EBP

complications, atherosclerosis, cardiovascular aging and skin pathologies, just to name a few. In this synopsis we will review the evidence supporting the beneficial effects of pharmacological PARP inhibitors in these diseases/pathologies and propose repurposing PARP inhibitors already available for the treatment of various malignancies.

1. Introduction

Lipid disorders are among the most severe threats to health globally. Obesity and high cholesterol levels are listed by the World Health Organization (WHO) as top risk factors associated with chronic (non-communicable) diseases that account for 60% of all deaths worldwide [1]. The family of PARPs and tankyrases (TNKS) are involved in numerous physiological processes vital to organismal homeostasis. The first associations between PARP1 and metabolic homeostasis came from the late 1990s and early 2000s [2–7], followed later by observations on association with lipid metabolism [7–11]. Since then, a mounting body of evidence demonstrate that the genetic deletion or pharmacological inhibition of PARPs is generally beneficial in lipid metabolism-related diseases, suggesting a wide-spread impact of these proteins on lipid-regulating pathways.

2. The enzymology and pharmacology of the PARP/ARTD family

PARP and TNKS enzymes are ADP-ribosyltransferases (ARTs). They perform ADP-ribosylation, which is a post-translational modification of proteins. Oxidized nicotinamide adenine dinucleotide (NAD^+) cleavage provides the building blocks for ADP-ribosylation resulting in the covalent attachment of one ADP-ribose unit [ADPR], oligo or polymers of ADP-ribose units [poly(ADP-ribose) (PAR)] to serine, glutamate, aspartate, arginine and lysine residues of target proteins [12–18].

There are 17 identified members of the PARP family in human, sharing a conserved catalytic domain, but possessing different structural domains, functions and cellular localizations [19–21] (Table 1). In our manuscript we applied the latest nomenclatural convention to designate enzymes [21]. PARP1, PARP2 and the two tankyrases (TNKS1 and TNKS2) perform actual poly(ADP-ribosyl)ation (PARylation), other PARPs catalyze mono(ADP-ribosyl)ation (MARylation) or oligo(ADP-ribosyl)ation, while PARP13, according to our current understanding, is enzymatically inactive [16]. The majority of total cellular PARP activity (85–90%) is determined by PARP1, while the rest is mostly attributed to PARP2 [22,23]. Although, the primary targets of PARP1's enzymatic activity include PARP1 itself, core histone proteins and transcription factors [24–27], a plethora of other PARylated proteins have also been identified by state-of-the-art mass spectrometry-based methods [14,17,28–33]. PARylated proteins can be accessed via the ADPriboDB database [34]. A recent study [35] suggested that the length and the level of branching in the PAR polymer determines the biological effectiveness in eliciting cellular responses to PARylation [35].

Poly(ADP-ribose) glycohydrolase (PARG), ADP-ribosyl-acceptor hydrolase-3 (ARH3) or ADP-ribosyl lyase degrades PAR polymers, creating a full substrate circle for PAR [40–42]. PAR turnover is extremely rapid,

Table 1
The main features of PARP enzymes.

PARP enzyme	Main enzymatic activity	Intracellular localization	Tissue expression	Ref.
PARP1	Poly	Nucleus; nuclear envelope; mitochondrion?; nucleolus; membrane?	Ubiquitously expressed, highest expression in lymph node, appendix, brain, placenta, prostate, spleen, testis	[21,36–39]
PARP2	Poly	Nucleus; nucleolus	Ubiquitously expressed, highest expression in brain, testis and adrenal gland	
PARP3	Mono	Nucleus; centriole?; cytoplasm; intercellular bridge	Ubiquitously expressed, highest expression in duodenum and small intestine	
PARP4	Mono	Nucleus; exosomes; cell membrane; spindle; cytoplasm	Ubiquitously expressed, highest expression in colon, duodenum and gall bladder	
TNKS	Poly	Nucleus; telomeres; Golgi; cytoplasm; nuclear membrane; spindle; pericentriolar material	Ubiquitously expressed, highest expression in testis and brain	
TNKS2	Poly	Nucleus; telomeres; Golgi; cytoplasm; nuclear envelope; pericentriolar material	Ubiquitously expressed, highest expression in thyroid gland	
PARP6	Mono	Cytoplasmic?	Ubiquitously expressed, highest expression in testis	
PARP7 (TiPARP)	Mono	Nucleus; cytoplasm	Ubiquitously expressed, highest expression in adrenal gland	
PARP8	Mono	Unknown cytoplasm?	Almost ubiquitous expression, high expression in bone marrow and thyroid gland	
PARP9	Mono	Nucleus; cell membrane; cytoplasm; mitochondrion	Ubiquitously expressed, highest expression in spleen and appendix	
PARP10	Mono	Nucleus; cytoplasm; Golgi; nucleolus	Ubiquitously expressed, highest expression in spleen	
PARP11	Mono	Nucleus; nuclear envelope; cytoplasm	Ubiquitously expressed, highest expression in lymph node and prostate	
PARP12	Mono	Nucleus	Ubiquitously expressed, highest expression in duodenum and small intestine	
PARP13 (ZC3HAV1)	Inactive	Nucleus; cytoplasm	Ubiquitously expressed, highest expression in bone marrow	
PARP14	Mono	Nucleus?; cytoplasm; cell membrane	Ubiquitously expressed, highest expression in spleen	
PARP15	Mono	Nucleus; cytoplasm?	Almost ubiquitous expression in spleen and lymph node	
PARP16	Mono	Cell membrane; endoplasmic reticulum; nuclear envelope; cytoplasm	Ubiquitously expressed, highest expression in ovaries	

Annotations for location or function that were inferred from only electronic data were omitted.

hence PAR has very short half-life [40–42]. Macrodomain-containing proteins can recognize and bind to ADPR units and, consequently, initiate cellular signaling events or can act as ADP-ribosyl hydrolases [43–46]. Based on these, Karlberg and colleagues [47] suggested the grouping of enzymes in ADP-ribose metabolism as "writers", enzymes synthesizing mono, oligo or poly ADPR chains (e.g. PARP enzymes or other ADP-ribosyl-transferases), "erasers" cleave off or degrade ADPR units or polymers from proteins (PARG, ARH3 or ADP-ribosyl lyase) and "readers" that can recognize ADPR units, bind to them and elicit biological responses (macrodomain-containing proteins or certain DNA repair factors).

PARP activity can be regulated by DNA damage and changes to chromatin structure [48–53], a set of posttranslational modifications and cellular signaling events [54,55]. Furthermore, NAD+ availability is a key factor to maintain PARP activity. Either competition with other NAD + -consumers as sirtuins [56], or local, compartmental supply of NAD+ for PARPs by nicotinamide/nicotinic acid mononucleotide adenylyltransferases (NMNATs) [57–60] is vital to sustain PARP activity.

Several pharmacological PARP inhibitors are available either for preclinical or clinical use. The Food and Drug Administration (FDA) or the European Medicines Authority (EMA) approved inhibitors (Olaparib, Rucaparib, Niraparib, Talazoparib, and Veliparib) are considered pan-PARP inhibitors that block all major PARP enzyme isoforms [61]. Currently these PARP inhibitors are used in various oncological indications with favorable side effect profile. Importantly, based on emerging evidence the potential clinical applicability of these inhibitors is far beyond the treatment of various malignancies [62–65]. There are also highly specific inhibitors for minor PARP enzymes (e.g. tankyrases or PARP10) in preclinical development.

PARPs are involved in a plethora of biological processes/functions, of which we will briefly mention only the ones that are of immediate importance for understanding our review, for the rest we refer readers to excellent comprehensive reviews [19,20,36,66,67]. PARPs play vital role in DNA repair and in the maintenance of chromatin structure [51,68–70].

Besides its crucial role in DNA repair, PARP1 regulates major cellular processes such as inflammation. PARP1 is considered proinflammatory in Th1 and Th2-mediated inflammatory reactions [71,72]. The proinflammatory role of PARP1 has been demonstrated in numerous clinically relevant large animal disease models [71,72], as well as in a human study [73] directly pointing towards human translation potential. Nevertheless, the role of PARP1 remains elusive in Th17-mediated pathologies [74–77]. PARP1 promotes inflammation through direct or indirect interactions with a large set of proinflammatory transcription factors, of which the key one is nuclear factor κB (NFκB) [78,79]. NFκB activation signals can be widespread, from classical cytokines, chemokines, through reactive oxygen/nitrogen species to pathogen-associated molecular patterns (e.g. endotoxins, flagellin), but in all cases, NFκB activation depends on PARP1 activation. It is of note that metabolic diseases are often associated with inflammation in which PARP1 activation has a key role. In certain diseases that are discussed in this review (e.g. alcoholic/non-alcoholic fatty liver disease or atherosclerosis) vascular inflammation is a major driver in the early stage of the pathology and is often triggered by bacterial products translocated to circulation through the leaky gut [80,81]. PARP1 inhibition improves the diversity of the gut microbiome in mice [82,83] that may support lower immunogenicity and a better outcome in these scenarios.

PARPs also have important roles in regulating cellular bioenergetics [84] and, linked to that, in the regulation of cell death [85–87]. PARP1 activation can largely reduce cellular NAD+ content [88–91]. Consequently, the resynthesis of NAD+ consume large amounts of ATP that leads to an energetic crisis leading to mitochondrial dysfunction [6,92]. The deletion of PARP1 can boost NAD^+ content in brown adipose tissue or skeletal muscle by 1.5–2 fold [91] highlighting an important role of PARPs in NAD^+ catabolism [93–95]. PARP1 activation can also suppress glycolysis further aggravating cellular energy crisis [96,97]. PARP1 activation, therefore, can strongly limit NAD^+ availability in cells [88,91], and subsequently can limit utilization of NAD^+ by other NAD + -dependent enzymes, such as sirtuins [56]. Genetic or pharmacological inhibition of PARP1 leads to mitochondrial biogenesis [91]. PARPs may also interfere with a large set of energy stress sensor enzymes (mammalian/mechanistic Target of Rapamycin Complex 1/2 (mTORC1/2), AMP-activated protein kinase (AMPK), etc.) (reviewed in [84]). Minor PARP enzymes, as PARP3, tankyrases or PARP10 are also implicated in regulating energy sensors and mitochondrial activity [98–101].

Mitochondrial PARylation is an ambiguous issue in terms of the role of PARPs in mitochondrial activity. Multiple PARylated proteins were identified in the mitochondria (reviewed in [102]). Importantly, the enzymatic activity for the removal of ADPR moieties was confirmed [103], however, the existence of PARylating activity in the mitochondria is still debated [104]. A recent study [105] suggested that PARylation takes place outside the mitochondria and proteins are imported into the mitochondria in a PARylated form. PARP7 localizes to the mitochondrial matrix, hence PARP7 may also be an alternative source of ADP-ribose [106]. To date, the debated issues are not cleared.

Energetic failure of cells can induce cell death. Pathological states that are characterized by reactive oxygen/nitrogen species production (e.g. inflammation, reperfusion injury, neurodegeneration, etc.) are characterized by PARP1 activation and excessive cell death via necrosis. There is ample data suggesting that PARP1 inhibition can either prevent cell death or divert necrosis into apoptosis [85,89,107,108]. Converting a necrotic-type cell death to a controlled apoptotic-type has numerous advantages, one of which is apoptosis being less inflammatory. A form of PARP activation-associated cell death was termed parthanatos [86,87,109,110].

In a closely related fashion to mediating mitochondrial activity and biogenesis, PARPs are also involved in metabolic regulation (reviewed in [111–113] of which we will review the aspects of lipid metabolism.

3. Modulation of the expression and activity of PARPs by lipid metabolites, metabolic hormones and lipids, lipotoxicity

Lipid molecules were shown to modulate the activity and expression of PARP1 and PARP2 (Table 2). Among these molecules we can find spontaneous oxidation products of cholesterol that activate PARP1, as 7-ketocholesterol (7KC) [8,10,114] and 15a-hydroxicholestene (15-HC) [115], as well as, inhibitors as 25-hydroxycholesterol [116]. Oxidized cholesterol derivatives induce PARP1 through triggering oxidative stress and consequently inducing DNA damage [117,118] or, as 15-HC, through activating Toll-like receptor-2 (TLR2) [115]. Furthermore, these spontaneously formed toxic cholesterol derivatives together with oxidized LDL (oxLDL) have key roles in PARP-mediated progression of atherosclerosis [10,114,119]. In good agreement with these observations, in mouse/rat models of bile duct ligation-induced cholestasis PARP1 overactivation was observed in liver and/or kidneys [120,121].

Cholesterol serves as a starting material for the biosynthesis of steroid hormones, vitamin D or bile acids. There is a strong bidirectional connection between sex steroids and PARP activity that is detailed in Chapter 4.3. Vitamin D is a suppressor of PARP1 activity [122], while it is an inducer of PARP2 expression [123]. Lithocholic acid and deoxycholic acid, two secondary bile acids can inhibit PARP2 expression [123].

Fatty acids and fatty acid-derivatives are also involved in regulating PARP activity. Caloric restriction reduces, while a high-fat diet or the overexpression of fatty acid synthase induces the expression or activity of PARP1 [91,124–127]. Fatty acids, as suberoylanilide hydroxamic acid (SAHA or Vorinostat), valproic acid (VPA) or butyrate can inhibit PARP activation and sensitize cells to PARP inhibitors [128,129]. Although, the mechanism of action for these fatty acids is unknown, these fatty acid-derivatives can act as histone deacetylase (HDAC) inhibitors and through that can interfere with PARPs in regulating gene expression

Table 2
Lipid molecules modulating PARP activity.

Lipid species	PARP	Model	Ref.
Inhibitors			
25-hydroxycholesterol	PARP1 activity	Ischemia-reperfusion injury in mice	[116]
Vitamin D		Mice treated with dihydrotestosterone	[122]
17-beta-estradiol	PARP(1) activity	Endotoxin-induced liver injury in mice	[154]
		Estrogen treatment reduces PARP(1) activity in the liver of female mice	[155]
		Murine model of autoimmune nephritis	[156]
Docosahexenoic acid		Rat model of neuroinflammation	[157]
		Neuronal cell line (HT22)	[158]
Tamoxifen		Ovariectomized rats	[159]
Raloxifen			
α-lipoic acid	PARP2 expression	Rat angiotensin-II induced heart failure model	[130]
Medroxyprogesterone		C2C12 murine myoblasts	[123]
Tibolone			
Lithocholic acid			
Deoxycholic acid			
Activators			
7-ketocholesterol	PARP1 activity	Microglia	[8]
		HUVEC cells	[10]
		Murine model of atherosclerosis	[114]
Dihydrotestosterone		Mice treated with dihydrotestosterone	[122]
17-beta-estradiol		Estrogen treatment induces PARP(1) activity in the peripheral blood mononuclear cells of female mice	[155]
		MDA-MB-231 breast cancer cells	[136]
15α-hydroxicholestene		Murine model of multiple sclerosis	[115]
Oleic acid		HepG2 cells	[140–142]
CCl_4		PARPi-treated mice	[121]
oxLDL		HAEC cells	[119]
Trichostatin A (TSA)		A549 cells	[160]
Valproic acid (VPA)			
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)		MDA-MB-231 breast cancer cells	[136]
Perfluorooctanoic acid	PARP1 expression	Murine embryogenesis model	[161]
		Murine liver	[132]
Simvastatin		Ionizing radiation in mice	[162]
Estrogen+progesterone		Murine model of embryo implantation	[163]
Vitamin D	PARP2 expression	C2C12 murine myoblasts	[123]
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	PARP7 activity	Hepa1c1c7 cells	[144]
		Chick embryo hepatocytes	[151,152]
		Rat H4IIE cells	
		T-47D cells	[149]
		HuH-7 cells	
		PARP7 knockout mice	[133]
3-Methylcholanthrene		PARP7 knockout mice	[148]
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	PARP7 expression	PARP7 knockout mice	[145]

Numbers in brackets refer to a likely target PARP enzyme for the lipid species.

patterns [129]. The α-lipoic acid, a mitochondrially synthesized heterocyclic fatty acid, can inhibit PARP2 expression [130]. Furthermore, serum lipids can boost PARP2 expression and alter its cellular localization [131].

PARP activation may also play a role in lipotoxicity (e.g. in alcoholic and non-alcoholic fatty liver disease (AFLD/NAFLD)) and in toxic injury (e.g. CCl_4 toxicity or environmental pollutant endocrine disruptors of lipid character) [121,132–136]. The pathways leading to PARP induction in lipotoxicity are depicted on Fig. 1. Common underlying mechanism of lipotoxicity is the induction of oxidative stress [137] that leads to DNA breaks and consequent PARP activation [138–142]. *De novo* lipid biosynthesis is mechanistically linked with PARP activation and the subsequent activation of extracellular signal-regulated kinases (ERKs) [138,139]. In good agreement with these, PARP1 is activated upon high-fat feeding [91,127,143].

Lipotoxicity-induced PARP activation in liver leads to decreases in NAD^+ levels [140,141] that inhibits SIRT1 and liver X receptor (LXR)α expression, insulin receptor and AMP-activated kinase (AMPK) activation that are key elements for hepatocyte viability [141]. PARP7 (TiPARP) can be activated by dioxins [144,145], tryptophan metabolites [146], short chain fatty acids [147] or other polycyclic aromatic compounds [148]. PARP7 is a repressor of aryl hydrocarbon receptor (AHR), suppressing the detoxification of toxic lipid species [133,149,150]. Active PARP7 acts as a metabolic disruptor by blocking hepatic gluconeogenesis [151,152], inducing the degradation of peroxisome proliferator activated receptor cofactor-1α (PGC-1α) [151], promoting LXR activity and eventually supporting hepatic lipid accumulation [153]. Consequently, PARP inhibition was shown to be protective against lipotoxicity [140,141].

4. Interaction of PARPs with transcription factors regulating lipid homeostasis

4.1. Nuclear PARPs and mechanisms of transcriptional regulation

Lipid metabolism in different cellular contexts is dynamically regulated by the concerted and integrated actions of a number of transcription factors (TFs) [164]. Several PARP enzymes have been implicated in transcriptional regulation [101,165,166]. Below, we discuss the modes of transcriptional regulation by PARPs with a focus on PARP1. PARP1 has been shown to regulate transcription through ADP-ribosylation of TFs, coregulators, histones, histone-modifying enzymes, and RNA polymerase II-regulating factors, among others [167–170], in which catalytic activity-independent roles were also identified [167,171–174]. Overall, the PARP1-dependent regulation of transcription can be broadly categorized as effects on (1) TF activity, (2) the chromatin landscape, and (3) RNA polymerase II-regulating factors.

4.1.1. Effects on TF activity

PARP1 has been shown to interact with and modulate the activity of multiple TFs, such as p53, B-MYB, AP-2, NF-κB, and hypoxia inducible factors (HIF) [172,175–178]. Although a number of NRs are regulated by PARP1, differences in the modes and mechanisms of regulation underscore the array of approaches used by PARP1 for regulating transcription. For example, the NR estrogen receptor alpha (ERα) is ADP-ribosylated by PARP1, leading to an increase in hormone-dependent ERα transactivation and subsequent target gene expression [179]. On the other hand, although androgen receptor (AR) is not ADP-ribosylated, PARP1 drives AR binding to chromatin and supports activation of AR-dependent genes, which in turn promotes prostate cancer growth [180]. Regulation of progesterone receptor (PR)-dependent gene expression has been shown to involve conversion of ADPR generated by PARP1 to ATP by the enzyme NUDIX5 [181]. The ATP potentiates nucleosome remodeling by ATP-dependent remodeling factors and activation of PR target genes in breast cancers [181]. PARP1 can also play a role in facilitating the exchange of transcriptional cofactors on NRs [182,183]. Taken together, these examples highlight some of the distinct mechanisms by which gene expression can be altered by PARPs.

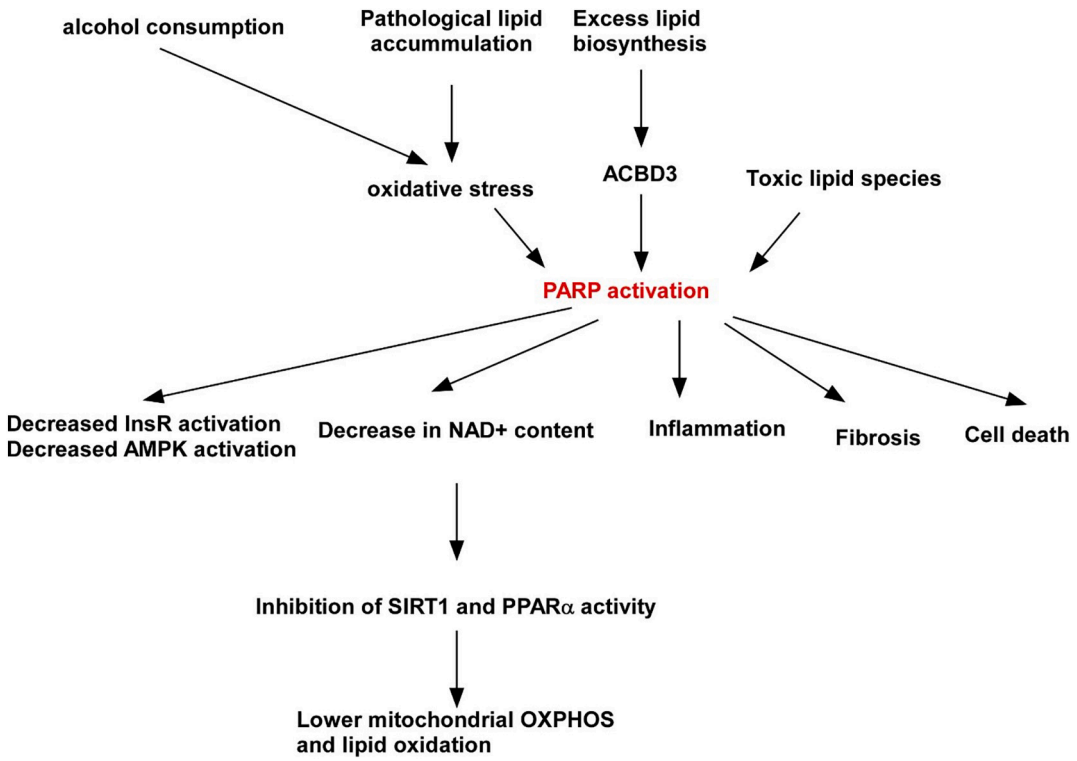

Fig. 1. General pathways of lipoto xicity.
Abbreviations: ACBD3 - acyl-CoA-binding domain containing 3, AMP-activated protein kinase (AMPK), InsR – Insulin receptor, OXPHOS – Oxidative phosphorylation, PPARα – Peroxisome proliferator-activated receptor alpha

4.1.2. *Effects on chromatin*

One of the first ways in which nuclear PARPs were shown to regulate gene expression was through the modulation of chromatin structure [184]. This is achieved by ADP-ribosylation of histones, as well as chromatin-associated proteins [168,185–187]. Histones were one of the first substrates identified for ADP-ribosylation [185]. PARP1 activation in response to heat shock can lead to a 'loosening' or expansion of chromatin in *Drosophila* polytene chromosomes, possibly through ADP-ribosylation of histone H1 [188,189]. ADP-ribosylation can interfere with other PTMs on histones, for example, ADP-ribosylation of histone H3 can prevent its methylation by Set7/9 histone methyl transferase, which then allows Set 7/9 to methylate histone H1.4 instead [190].

Despite a large body of evidence showing the importance of histone ADP-ribosylation in the regulation of gene expression, the mechanisms underlying the interactions between PARPs and histones, specificity of target selection, and physiological triggers for histone ADP-ribosylation remain to be determined. Recent work has identified histone PARylation factor 1 (HPF1) as an accessory protein that helps switch PARP1 activity from automodification to transmodification of histones [170]. Interestingly, PARP1 can also ADP-ribosylate histone-modifying enzymes, such as the histone lysine demethylase KDM5B, as well as ATP-dependent remodeling factors, such as or ALC1 and ISWI nucleosome remodelers, which can lead to altered chromatin structure [191–194]. Thus, multiple chromatin constituent proteins and associated proteins are regulatory substrates for ADP-ribosylation. An interesting feature of PARP1 and PARG in NR-dependent promoter activation is a role in assisting the resealing of the DNA strand breaks created by the activation of topoisomerase II to relieve DNA stress [183,195–197]. Through these mechanisms, PARPs can regulate heterochromatin/euchromatin switch and gene accessibility [198].

Although we have only presented a brief overview here, gene regulation by PARPs has been discussed in greater detail in other reviews [168,184,199,200].

4.2. NAD^+, PARPs, ADP-ribosylation, and transcriptional regulation in lipid homeostasis

A number of studies have illustrated the role of PARPs in regulating lipid homeostasis through transcriptional modulation. A key question regarding gene regulation by PARP1 and PARP2 is what are the mechanisms and factors that control their catalytic activity.

4.2.1. *Stimulation of PARP catalytic activity*

The activation of PARP1 and PARP2 catalytic activity by damaged DNA under genotoxic stress and during DNA damage responses is well characterized [201]. But, many aspects of lipid homeostasis regulation occur under physiological conditions. What may activate PARP1 and PARP2 catalytic activity under those conditions? In addition to the above-mentioned lipid species, PARP1 catalytic activity is regulated through allosteric mechanisms involving non-pathological binding partners (e.g., nucleosomes, snoRNAs, and an assortment of nuclear proteins) and PTMs (e.g., phosphorylation by Erk1/2) [68,199,202,203]. Similar mechanisms may be used by PARP2, but they are less well characterized. In addition, PARP2 can be activated by RNA species [204].

4.2.2. *Activation of PARP1 by snoRNAs*

Recently, a novel role for short nucleolar RNAs (snoRNAs) as activators of PARP1 catalytic activity has been discovered [18,203,205]. This newly discovered mode of regulation has the potential to regulate PARP1 catalytic activity in a number of physiological conditions – besides, the highly regulated levels of snoRNA in many cell types makes it even more flexible. Indeed, in 3 T3-L1 cells, a subset of snoRNAs exhibiting adipogenic expression patterns that correlate with the levels of nuclear ADP-ribosylation, are able to stimulate PARP1 activity [18]. Additionally, depletion of these snoRNAs results in attenuated ADP-ribosylation and increased adipogenic gene expression. Interestingly, NMNAT-1, a nuclear NAD^+ synthase, acts independently of its catalytic

activity to potentiate ADP-ribosylation of substrates by snoRNA-activated PARP1 [18]. Overall, this represents a new mode of physiological regulation of PARP1 catalytic activity during adipogenesis that may also have broader impact on PARP1 biology.

4.2.3. *Role of NAD$^+$ levels in regulating PARP catalytic activity*

PARP catalytic activity is dependent on the substrate, NAD$^+$ [167,206,207], therefore, changes to NAD$^+$ availability impact PARP activity. NAD$^+$ synthesis in the different cellular compartments is regulated by the NMNAT family of enzymes, with NMNATs 1, 2, and 3 being localized to the nucleus, cytosol and mitochondria respectively [58,208]. The role for local NAD$^+$ salvage pathways has been implicated in the regulation of PARP1 activity [59,60,95,209,210]. However, supplementing cells with nicotinamide riboside, a precursor of NAD$^+$ did not influence PARP activity in unstressed cells or tissues [211]. Furthermore, changes to NAD$^+$ salvage in the nuclear and cytosolic compartments through the differential regulation of NMNATs can largely impact PARP1-mediated transcriptional events [59]. In other words, while the overall cellular levels of NAD$^+$ remain unaffected, compartment specific NAD$^+$ biosynthesis dramatically alters PARP1 activity and subsequently affect transcriptional outcomes in adipocytes [59]. It is of note that PARP1, by limiting NAD$^+$ for other NAD$^+$-dependent enzymes, as sirtuins, can modulate transcriptional programs elicited by these enzymes (for review see [56,93,212]).

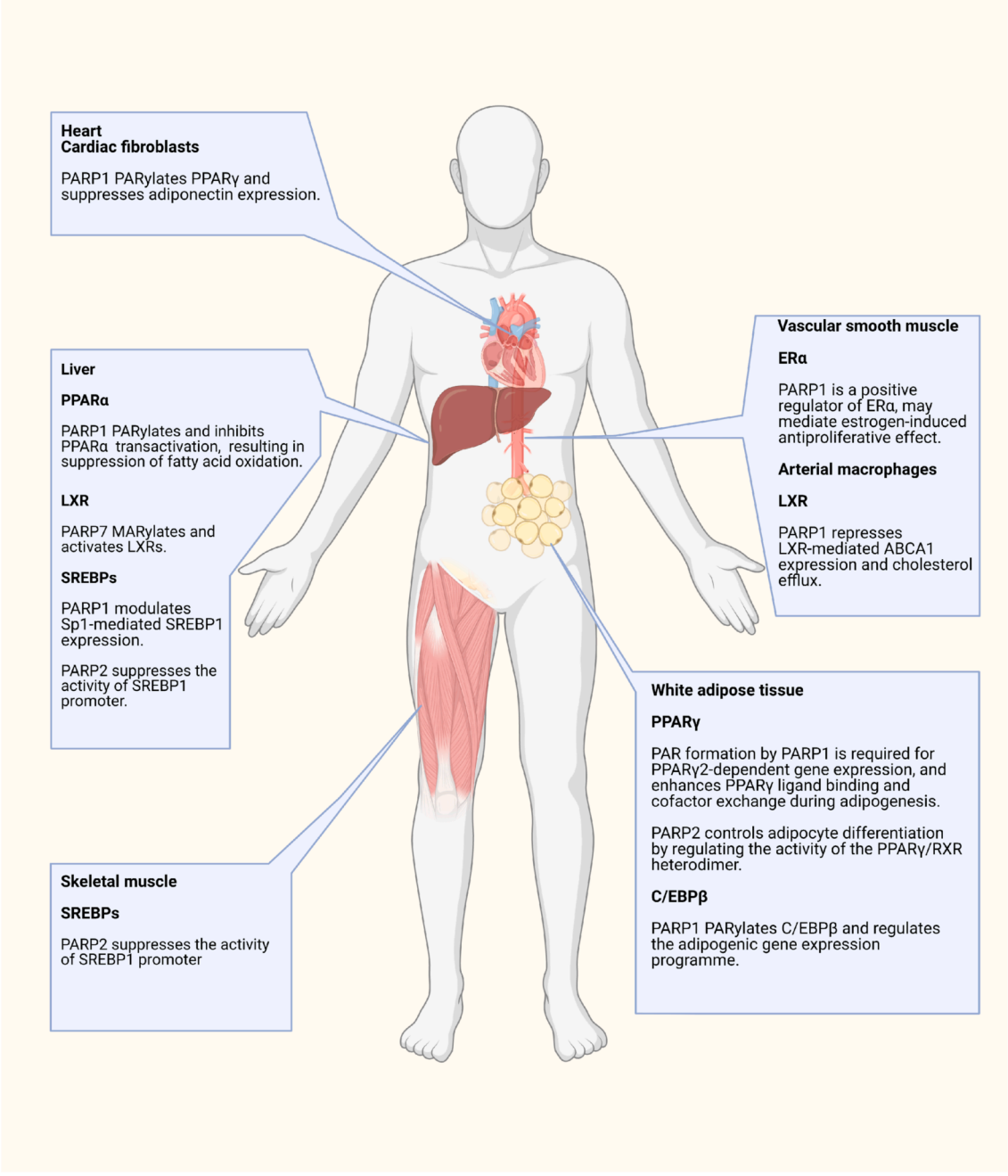

Fig. 2. Interactions between transcription factors and PARP enzymes.
Abbreviations: C/EBP - CCAAT-enhancer-binding proteins, SREBP - *Sterol regulatory element-binding protein, PPAR – peroxisome proliferator activated receptor, LXR – liver X receptor, ER – estrogen receptor*

4.3. PARPs and lipid-activated nuclear receptors

As previously discussed, PARP-dependent regulation of nuclear receptor (NR) function has been shown to impact numerous biological processes, including metabolic signaling (Fig. 2). The interactions between PARP enzymes and key lipid-responsive NRs will be discussed in this chapter without detailed discussion of the interactions between PARP1 and progesterone receptor [213], androgen receptor [180,214–216], estrogen receptor [179,195], thyroid hormone receptor [217], retinoid A receptor [182], neuron-derived orphan *receptor* 1 (*NOR1*) [218] and the glucocorticoid receptor (GR) [219]. Most of the receptors mentioned below respond to stimulation by lipids (e.g. cholesterol, retinoic acid, oxLDL etc.) and their downstream effects impact on lipid metabolism. Importantly, the dysregulation of these transcription factors are frequent in the pathologies of lipid metabolism, such as atherosclerosis [220], obesity [221], AFLD and NAFLD [222,223].

4.3.1. PPARγ

PPARγ is one of the predominant lipid-activated NRs involved in adipocyte differentiation, with fat-specific PPARγ depletion in mice affecting all adipose tissue depots, including both white and brown adipose tissues [224,225]. PPARγ binds to thousands of sites across the genome, including genes involved in glucose and lipid metabolism, usually as a heterodimer with RXR [226]. PPARγ binding sites overlap significantly with C/EBPα binding sites, suggesting that these two transcription factors can act cooperatively to induce adipocyte gene expression program, specifically in terminal differentiation [226]. Inhibition of PARP1 with small molecule PARP inhibitors attenuates the expression of the PPARγ-dependent genes aP2, CD36, and adiponectin in the later stages of adipogenesis, which may antagonize PARP1 recruited to PPARγ binding sites in a topoisomerase II-dependent manner [183]. Adiponectin expression in cardiac fibroblasts also requires PARP1, specifically through the ADP-ribosylation of PPARγ [227]. In addition, PARP1 catalytic activity may drive the activation of PPARγ-dependent gene expression by facilitating the exchange of the PPARγ co-repressor NCoR1 for the co-activator p300 [183] (Fig. 3).

In addition to PARP1, other PARP family members, such as PARP2, have been shown to regulate PPARγ transcriptional activity, as well. PARP2 interacts with PPARγ/RXR heterodimers and is needed for basal PPARγ activation. Indeed, loss of PARP2 results in decreased expression of PPARγ target genes, as well as impaired differentiation of mouse embryonic fibroblasts into mature adipocytes [228].

(*Top*) PARP1-dependent regulation of TF and chromatin in adipocytes. PARP1-mediated ADP-ribosylation of C/EBPβ inhibits its DNA binding and prevents activation of the C/EBPβ transcriptional program in undifferentiated cells. PARP1-mediated ADP-ribosylation of histone H2B on glutamate 35 (E35) attenuates phosphorylation on the neighboring serine residue (S36). Reduced E35 ADP-ribosylation upon differentiation leads to increase S36 phosphorylation and pro-adipogenic gene expression. PARP1 is recruited to DNA-bound PPARγ and enables the binding of the co-activator p300. This potentiates the expression of PPARγ target genes.

(*Bottom*) PARPs regulate lipid metabolism by modulating hepatic gene expression. PARP1-mediated ADP-ribosylation of PPARα can impede its ability to activate target gene expression in hepatocytes. PARP2 binds to the promoter of the *Srebp1* gene and inhibits its expression. SREBP1 is a key TF involved in hepatic metabolism. Thus, by modulating SREBP1 expression, PARP2 can regulate liver-specific gene expression.

4.3.2. PPARα

PPARα is a lipid-activated NR that is integral to lipid homeostasis, particularly in the liver, where it modulates lipid storage in hepatocytes [229]. PPARα also regulates gluconeogenesis, amino acid metabolism, and inflammatory responses. Loss or inhibition of PPARα exacerbates NAFLD and helps the progression to non-alcoholic steatohepatitis (NASH) [230,231].

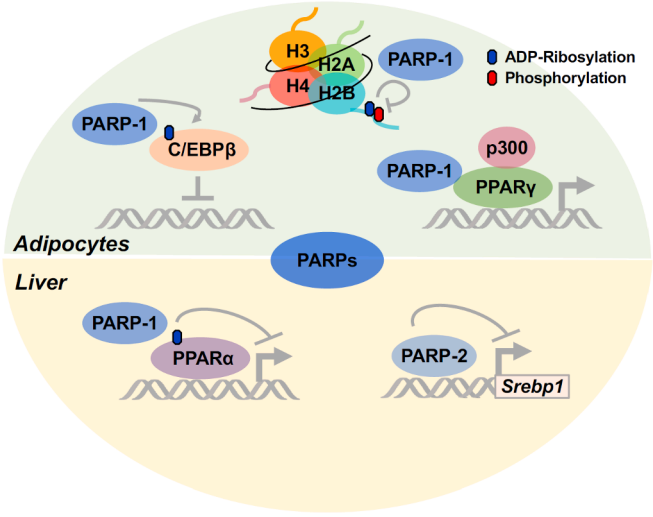

Fig. 3. Differential roles of PARPs in gene regulation in adipocytes and liver.

PARP1 can directly ADP-ribosylate PPARα, which in turn inhibits its transactivation attenuating the expression of fatty acid oxidation genes, thereby, leading to hepatic steatosis (Fig. 3). SIRT1 is an important cofactor of PPARα [232]. PPARα ADP-ribosylation dissociates PPARα from SIRT1 preventing its recruitment to target promoters [127]. In fact, as both PARP1 and SIRT1 compete for NAD^+, their relative activity can potentially fine-tune PPARα activity.

4.3.3. LXR

LXR is a NR involved in regulating cholesterol, lipid, and carbohydrate metabolism-associated genes. In a manner similar to PPARs, LXRs can heterodimerize with RXRs and form transcriptionally active complexes once stimulated by agonists [233]. In the liver, LXRs can regulate the expression of genes encoding proteins involved in lipogenesis, including the master regulator SREBP-1c [234]. LXRs regulate cholesterol efflux in macrophages, particularly in macrophages found at atherosclerotic plaques [234]. Additionally, LXRs can repress the expression of inflammatory genes in macrophages [233]. Although the mechanisms that regulate LXR activity in macrophages have not yet been completely investigated.

Using an unbiased mass spectrometric approach, Shrestha et al., found that PARP1 interacts with LXR and can ADP-ribosylate LXR in macrophages [235]. Moreover, PARP1 can suppress the expression of LXR target genes, including the gene encoding the cholesterol transporter ATP-binding cassette sub-family A Member 1 (ABCA1), and treatment of macrophages with PARP inhibitors leads to an increase in cholesterol efflux [235].

Interestingly, PARP-7, a nuclear and cytosolic mono(ADP-ribosyl) transferase, has been shown to ADP-ribosylate both LXRα and LXRβ subunits, as well as, acts as a co-activator for LXRs [153]. In line with that, Parp7 loss in mice correlated with the attenuation of expression of the LXR target gene, Srebp1. Interestingly, the ADP-ribosyl hydrolase, MACROD1, interacts with LXR in a PARP-7-dependent manner and inhibits PARP-7-mediated activation of LXR [153]. PARP-7 also contains an ADP-ribosyl hydrolase macrodomain, as well as a WWE PAR binding domain, suggesting that LXR regulation may involve interactions with different PAR-binding and PAR-hydrolyzing proteins.

4.4. Other lipid homeostasis-related transcription factors regulated by PARPs

In addition to the lipid-activated NRs described above, the following

TFs are also regulated by nuclear PARPs.

4.4.1. C/EBPβ

C/EBP family members (i.e., C/EBPα, C/EBPβ, and C/EBPδ), together with PPARγ, are indispensable for the regulation of adipocyte differentiation. The clonal commitment and differentiation phase of adipogenesis is characterized by the activation of C/EBPβ and C/EBPδ among other transcription factors, such as KLFs, CREB, and SREBP1c [236]. The activation of C/EBPβ is critical for triggering the terminal differentiation phase of adipogenesis by inducing the expression of C/EBPα and PPARγ [236]. In 3 T3-L1 cells, C/EBPβ binds extensively across the genome only a few hours post-differentiation and marks putative enhancer regions that open up the chromatin, allowing for binding of later adipogenic transcription factors, such as PPARγ [237].

4.4.2. Sterol regulatory-element binding proteins

SREBPs, SREBP1 and SREBP2 regulate the expression of genes involved in lipid synthesis [238–240]. SREBP activation through limited proteolysis is initiated upon low cholesterol levels. [240]. SREBP1 has two splice forms, SREBP1a and SREBP1c [241]. The SREBP isoforms have differential impact on cholesterol and fatty acid biosynthesis [242].

In hepatocytes, the inhibition of PARP1 leads to an increase in lipid synthesis, which is reflected by increased levels of SREBP1 expression [142]. Contradicting this observation, in AFLD, the pharmacological inhibition of PARP1 blocks the induction of SREBP1 [223]. PARP2 acts as negative regulator of SREBP1 expression [243] and in a similar fashion, as a negative regulator of SREBP1 and SREBP2 in skeletal muscle [123] (Fig. 3). Finally, PARP7 is a positive regulator of SREBP1 expression through the direct activation of LXR [153].

4.4.3. Peroxisome proliferator activated receptor cofactor-1α (PGC1α)

PGC1α is a nuclear receptor cofactor interfering with a plethora of metabolic pathologies. Single nucleotide polymorphisms in PGC1α were associated with type II diabetes and insulin resistance [244] and in type II diabetes patients, PGC1α-dependent genes were coordinately downregulated [245]. PGC1α drives, among others, mitochondrial biogenesis [246] and represses gluconeogenesis [151,247] that are responsible for the antidiabetic properties of PGC1α. PARP1, PARP2 and TiPARP inhibition induces the deacetylation and, hence, the activation of PGC1α [91,151,248] (Fig. 4). Tankyrases can PARylate and inhibit the transcriptional activity of PGC1α [101] (Fig. 4).

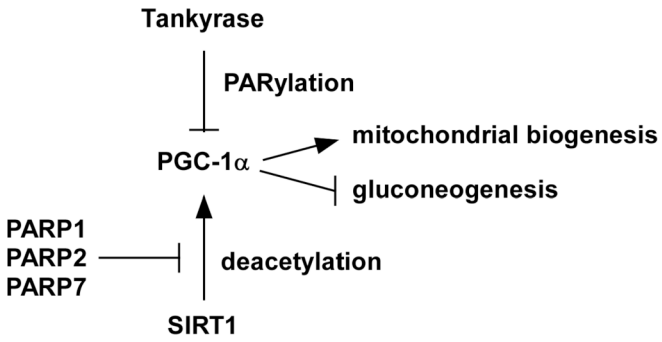

Fig. 4. PARP-dependent regulation of PGC1α.

5. Role of PARPs in main pathways of lipid metabolism and related pathologies

5.1. Fatty acid metabolism

Although comprehensive studies are missing, PARPs likely impact on fatty acid biosynthesis and transport. In terms of synthesis, the loss of PARP2 led to a drop in the expression of fatty acid synthase in white adipose tissue [228]. Furthermore, SREBP1, a transcription factor regulated by PARPs (see Chapter 4.3) [123,142,243], can promote fatty acid biosynthesis in murine and cellular models. The expression of the fatty acid transporters, FABP7, FABP3, CD36, and aP2 (FABP4), are regulated by PARP1, PARP2, and tankyrases in various tissues including the adipose tissue or the skin [100,197,228,249]. Lipophagy is a cellular source for triglycerides that was shown to be upregulated in a PARP1-dependent fashion upon UVB irradiation in cellular models [250]. PARP1, PARP2 and PARP10 were shown to be involved in the regulation of autophagy in cellular models [251–253] suggesting a possible involvement in regulating cellular lipophagy. Physiological and pathophysiological lipid storage and deposition will be discussed in subsequent chapters discussing the liver, adipose tissues and atherosclerosis (Chapter 5.2). The deletion or pharmacological inhibition of PARP1 or PARP2 modulates the composition of biomembranes that withhold considerable amounts of lipids. The deletion or inhibition of PARP1 altered the composition of membrane lipids in the skin [249] and erythrocytes [254], and interfered with the abundance of inflammatory polyunsaturated fatty acid metabolites in skin [249]. The deletion of PARP2 modified the composition of the membrane of cultured skeletal muscle fibers [123].

Fatty acids can be eliminated by oxidation in peroxisomes or mitochondria (the roles of PARPs in mitochondrial biology is comprehensively reviewed in [84]). Deletion or inhibition of PARP1 induces mitochondrial fatty acid oxidation genes as MCAD, L-CPT-1 [91] and leads to fatty acid oxidation [127,143] in murine models. Interestingly, UVC irradiation increased fatty acid oxidation that was dependent on the coordinated activation of PARP1 and AMPK, and pharmacological PARP inhibition abolished UVC-induced fatty acid oxidation in a murine model [255]. Deletion of PARP10 induces fatty acid oxidation in cellular cancer models [99]. Similarly to PARP10, the deletion of PARP2 can induce fatty acid oxidation in multiple tissues [248] that culminate in enhanced fatty acid oxidation at the level of the organism, marked by a reduced respiratory quotient throughout the diurnal cycle [248]. There are signs for enhanced fatty acid oxidation in the livers of tankyrase knockout mice marked by enhanced expression of ACO1, CPT1α, MCAD, PGC1α and increases serum ketone body levels [100]. In good agreement with that, the deletion of PARP1 or the pharmacological inhibition of tankyrases reduce serum triglyceride (TG) and serum non-esterified fatty acids (NEFA) in mice [101,256] (Table 2).

5.2. Cholesterol and lipoprotein homeostasis, hyperlipidemia, dyslipidemia, atherosclerosis

Cholesterol is either ingested from nutrients or is synthesized in the body, the liver being the central organ capable of synthesizing and distributing cholesterol for other organs and of diverting cholesterol for excretion. Cholesterol biosynthesis may take place in other organs and tissues (e.g. skeletal muscle), nevertheless, the cholesterol is utilized locally. Cholesterol from nutrients is taken up in the small bowels and is then transported to the liver through the portal circulation in the form of chylomicrons. The liver harvests chylomicrons and, hence, cholesterol. Excess cholesterol is excreted to the bile and subsequently to the small bowels. That circuit is termed the enterohepatic circulation of cholesterol. The liver distributes cholesterol by low density lipoprotein (LDL) to the peripheral organs through the circulation and excess peripheral cholesterol is collected by high density lipoprotein (HDL) and is taken to the liver. This circle is termed the peripheral circulation of cholesterol. It is of note that murine and human lipoprotein homeostasis has differences, as mice have little LDL, rendering HDL as a major peripheral cholesterol transporter in both directions. Cholesterol is a starting compound for the synthesis of steroid hormones, vitamin D, and bile acids. Multiple studies have linked PARP1 to cholesterol homeostasis, while a genome-wide association study has linked PARP2 to cholesterol metabolism [257]. PARP2 is associated with cholesterol biosynthesis, the deletion of PARP2 induces de novo cholesterol biosynthesis in the

skeletal muscle and in the liver through inducing the expression of SREBP1 and SREBP2 [123,243]. In murine skeletal muscle the increases in cholesterol biosynthesis increases intramuscular cholesterol levels and a portion of cholesterol accumulate in the membranes leading to restricted lateral diffusion in biomembranes [123].

To date, no PARP-dependent changes are known for chylomicron homeostasis. Hepatic and muscular cholesterol production in mice is under the influence of PARP2 activation through regulating SREBP1 [123,243]. Deletion or lower expression of PARP2 leads to accumulation of cholesterol in these tissues. Cholesterol export from the liver is dependent on ABCA1, a transport protein. Lower expression of ABCA1 reduces cholesterol flux into bile, as well as, towards LDL. The deletion of PARP2 reduced hepatic ABCA1 expression through a yet unknown mechanism in mice and HepG2 cells [243] (Fig. 5). PARP1 was shown to be a negative regulator of microsomal epoxide hydrolase (EPHX1) that is presumed to have a role in hepatic cholesterol transport and the low expression of which causes hypercholanemia in humans [258,259].

Genetic or pharmacological inhibition of PARP enzymes have beneficial effects in hyperlipidemia of different etiology as diabetes, high-fat feeding or high cholesterol feeding (Table 3). Most results point out that the inhibition of PARP1 or tankyrases reduce serum total cholesterol levels [101,260–262] and improve the HDL/LDL ratio [101,260–262]. The promoter of apolipoprotein D, a constituent of HDL, was shown to be positively regulated in NIH 3 T3 fibroblasts by PARP1 [263]. PARP inhibition reduces the atherogenic index in murine models [260,261] and improves vascular dysfunction [11,264]. Importantly, in humans, the SNP rs1136410, a non-synonymous SNP in PARP1 that reduced PARP activity was shown to correlate with changes to cholesterol homeostasis. The minor GG genotype, characterized by lower PARP activity, showed correlation with history of hyperlipidemia [265]. Individuals with GG genotype had lower total serum cholesterol and higher HDL levels [265]. These results suggest that the findings of the murine studies can be translated to humans.

The genetic deletion of PARP2 in mice reduced serum HDL levels [243], however, whether changes to HDL supports the anterograde or retrograde transport of cholesterol was not determined yet. Hepatic Apolipoprotein B (ApoB) secretion was dependent on PARP10, PARP10 silencing reduced the expression of ApoB in primary human hepatocytes [266]. PARP10 expression can potentially affect very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL levels and PARP10 falls into a genetic locus associated with LDL homeostasis [266]. PARP9 and PARP14 were suggested to be involved in hypercholesterolaemia and hyperlipidemia through regulating the expression of LDL receptor and certain apolipoproteins in macrophages [166].

It should be noted that while multiple studies have shown that lower PARP1 activity is associated with normalized HDL/LDL ratios and the normalization of hypertrigliceridaemia [262,265], a report from the laboratory of Michael Hottiger [268] showed an opposite phenotype and another report showed no changes to serum TG, LDL and HDL levels upon PJ34 treatment [142]. Interestingly, in a murine model of high cholesterol feeding the deletion of PARP1 led to higher cholesterol, LDL and HDL levels [256] suggesting that PARP1 may have adverse roles upon cholesterol overload.

Atherosclerosis is a disease affecting large human populations that is associated with disturbances to lipoprotein metabolism and atopic lipid accumulation to blood vessels called atherosclerotic plaques. The first step in atherosclerosis is the trapping of lipid species, namely lipoproteins, to modified glycosaminoglycan molecules on the intima of blood vessels [269,270] that is followed by an inflammatory stage followed by calcification and the formation of an atherosclerotic plaque [271,272]. There is evidence that in humans PARP activation is associated with the risk for atherosclerosis [265] and in murine models the pharmacological inhibition and/or deletion of PARP1 can lead to plaque regression [262] and/or increased plaque stability accompanied by improved endothelial function [11,264], highlighting the central role of PARP1 in this disease and providing a translational value.

Currently, there is evidence for the involvement of PARP1 in the inflammatory stage of the disease (for detailed reviews see [272–276]). PARP1 activation was demonstrated in human and murine atherosclerotic plaques [9,277]. PARP1 activation in the plaques is due to DNA strand breaks inflicted by oxidative and nitrosative stress [9,256,277,278] that is induced by inflammation [119,260], by

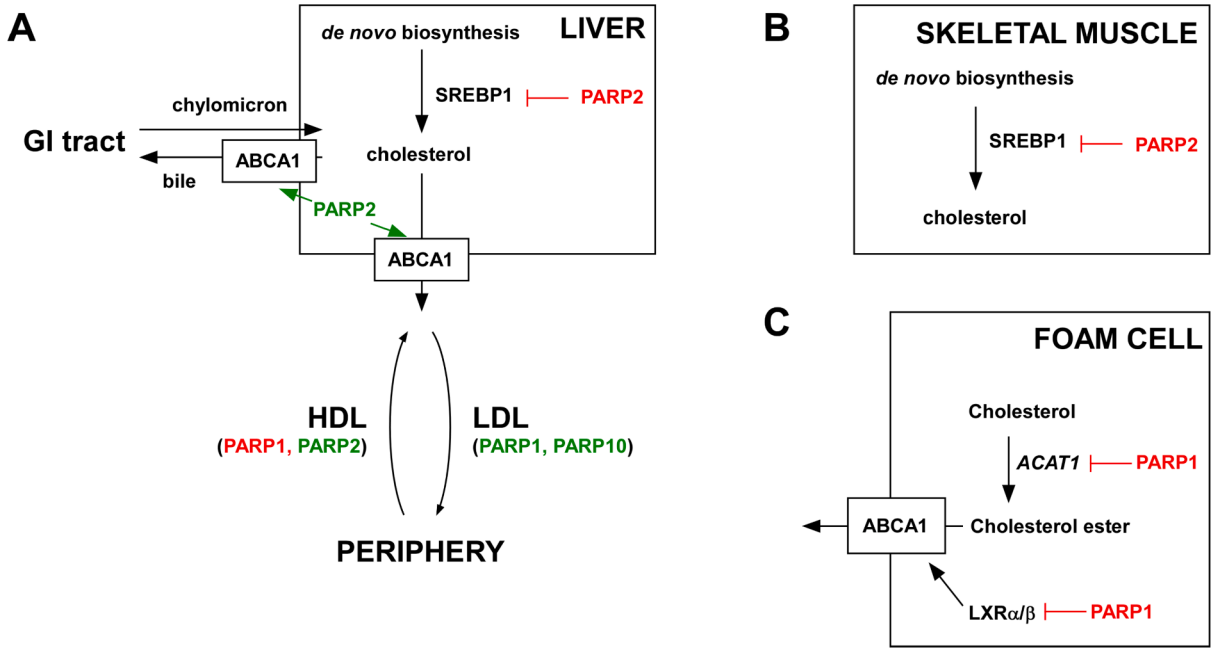

Fig. 5. The involvement of PARPs in the regulation of cholesterol homeostasis.
PARP-mediated regulatory points are highlighted in (A) liver, (B) skeletal muscle and (C) foam cell cholesterol homeostasis. Inhibitory effects are marked in red, while positive effects are in green. Abbreviations: ABCA1- ATP-binding cassette sub-family A Member 1, ACAT1 - mitochondrial acyl-coenzyme A/cholesterol acyltransferase-1, GI – gastrointestinal, HDL – high density lipoprotein, LDL – low density lipoprotein, LXR - liver X receptor, SREBP - sterol regulatory-element binding protein.

Table 3
Effects of PARP enzymes on serum/plasma lipid and lipoprotein levels.

Lipid	PARP enzyme	Model/effect	Ref.
TG	Tankyrase	Pharmacological inhibition by G-007LK decreases serum TG in *db/db* but not in *db/*$^{+}$ mice.	[101]
	PARP1	TG levels decreased in chow-fed ApoE$^{-/-}$ PARP1$^{-/-}$ mice.	[256]
	PARPi	TIQ-A treatment of ApoE−/− mice did not affect serum TG levels.	[11]
		INO-1001 treatment of ApoE−/− mice had a trend for lower TG levels in INO-1001 treated mice.	[267]
NEFA	Tankyrase	Pharmacological inhibition by G-007LK decreases serum NEFA in *db/db* but not in *db/*$^{+}$ mice.	[101]
glycerol	Tankyrase	Pharmacological inhibition by G-007LK decreases serum glycerol in *db/db* but not in *db/*$^{+}$ mice.	[101]
TC	Tankyrase	Pharmacological inhibition by G-007LK decreases serum TC in *db/db* but not in *db/*$^{+}$ mice.	[101]
	PARP1	The recessive GG allele of Rs1136410 SNP with lower PARP1 activity correlates with lower serum TC levels.	[265]
		The deletion of PARP1 reduced serum TC in HFD-fed mice.	[260]
		PARP1 knockout mice fed on HFD have higher serum TC levels as compared to wild type.	[268]
		The deletion of PARP1 induced serum total cholesterol levels in APOE$^{-/-}$ chow-fed mice. The deletion of PARP1 reduced serum total cholesterol levels in APOE$^{-/-}$ HFD-fed mice.	[261]
		TC levels are increased in HCD-fed APOE$^{-/-}$ PARP1$^{-/-}$ mice.	[256]
	PARPi	Pharmacological PARP inhibition by TIQ-A decreased plasma TC in chow-fed and HFD-fed mice.	[262]
		TIQ-A treatment of ApoE−/− mice did not affect serum cholesterol levels.	[11]
		INO-1001 treatment of ApoE−/− mice did not affect serum cholesterol levels.	[267]
LDL	PARP1	The deletion of PARP1 reduced serum LDL in HFD-fed mice.	[260]
		The deletion of PARP1 reduced serum total cholesterol levels in APOE$^{-/-}$ HFD-fed mice.	[261]
		LDL levels are increased in HCD-fed APOE$^{-/-}$ PARP1$^{-/-}$ mice.	[256]
	PARPi	TIQ-A treatment of ApoE−/− mice did not affect serum LDL levels.	[11]
		INO-1001 treatment of ApoE−/− mice had a trend for lower LDL levels in the INO-1001 treated group.	[267]
	Tankyrase	Pharmacological inhibition by G-007LK decreases serum LDL in *db/db* but not in *db/*$^{+}$ mice.	[101]
VLDL	PARPi	TIQ-A treatment of ApoE−/− mice did not affect serum VLDL levels.	[11]
VLDL^{+}LDL	PARPi	Pharmacological PARP inhibition by TIQ-A decreased plasma LDL^{+}VLDL cholesterol in chow-fed and HFD-fed mice.	[262]
HDL	PARP1	The recessive GG allele of Rs1136410 SNP with lower PARP1 activity correlates with higher serum HDL levels.	[265]
		The deletion of PARP1 increases HDL cholesterol levels in chow diet-fed ApoE−/− mice that was abolished by high-fat feeding.	[260].
		HDL levels are increased in chow-fed and HCD-fed APOE$^{-/-}$ PARP1$^{-/-}$ mice.	[256]
		The deletion of PARP1 induced serum HDL levels in APOE$^{-/-}$ chow-fed and HFD-fed mice.	[261]
	PARPi	TIQ-A treatment of ApoE−/− mice did not affect serum HDL levels.	[11]
		INO-1001 treatment of ApoE−/− mice had a trend for higher HDL levels in the INO-1001 treated group.	[267]
	PARP2	The deletion of PARP2 decreases serum HDL in chow-fed mice	[243]
	Tankyrase	Pharmacological inhibition by G-007LK decreases serum HDL in *db/db* but not in *db/*$^{+}$ mice.	[101]

Abbreviations: HCD- high cholesterol diet, HDL – high density lipoprotein, HFD – high-fat diet, LDL – low density lipoprotein, NEFA – non-esterified fatty acid, PARPi – PARP inhibitor treatment, TC - Total cholesterol -, TG – triglyceride, VLDL – very low density lipoprotein.

oxidatively modified cholesterol metabolites, as 7-ketocholesterol [8,10,114] or oxidized forms of LDL (oxLDL) [119,278] both in humans and murine models. In fact, the pharmacological inhibition of PARP1 can restore the activity of aldehyde dehydrogenase2 (ALDH2) in mice in the endothelium and in cultured endothelial cells that can convert oxidized lipid products, containing aldehyde groups, to less toxic forms [119].

Besides supporting inflammation [267,279,280], plaque calcification [281] and restenosis [282–284], PARP1 plays central role in regulating lipid metabolism and lipid-elicited effects (e.g. cell and tissue damage) in atherosclerotic plaques (Fig. 6). PARP1 activation can block the expression of ABCA1, a key enzyme in cholesterol export from foam cells through inhibiting LXR activation in macrophages [235]. Interestingly, in another study, ABCA1 was not regulated in foam cells and atherosclerotic plaques upon PARP inhibition with TIQ-A [262]. This discrepancy is yet unexplained. Furthermore, PARP inhibition with TIQ-A reduced the expression of mitochondrial acyl-coenzyme A/cholesterol acyltransferase-1 (ACAT1) in a murine model of atherosclerosis [262]. ACAT1 is necessary for the esterification of cholesterol [285] and in agreement with that observation, the deletion of PARP1 blocks the accumulation of esterified cholesterol to foam cells [114]. PARP1 plays role in cell and tissue damage induced by oxidized lipids in atherosclerotic plaques. In foam cells the deletion of PARP1 increased the proportions of apoptotic cells [114]. In turn, the deletion of PARP1 in smooth muscle cells protected cells against 7KC-induced caspase-dependent apoptosis and the induction of c-Jun N-terminal kinase (JNK) and induced ERK1/2 [114].

PARP9 and PARP14 are demonstrated to be involved in the development of human and murine atherosclerotic plaques [166]. Given their involvement in lipoprotein metabolism and inflammation, it is possible that other PARP enzymes, like PARP2 or tankyrases may also have important roles in regulating atherosclerosis development and lipid metabolism in atherosclerotic plaques [101,243].

5.3. PARP enzymes modulate steroid hormone biosynthesis and steroid hormone-elicited responses

The central organ for steroid hormone biosynthesis is the suprarenal (adrenal) gland and it is accompanied by organs specialized in the production of a subset of steroid hormones, such as the testes (androgens), skeletal muscles (androgens), ovaries (estrogens and progesterone), the white adipose tissue (estrogens) or the skin (all steroids). Steroid hormones are synthesized from cholesterol by the size reduction of the side chain of cholesterol and a subsequent oxidization of the gonane core yielding progesterone. Progesterone is then converted to either mineralocorticoids, glucocorticoids or androgens through the action of cytochrome P450 (cyp) enzymes (Fig. 7). Androgens can be then converted to estrogens by the enzyme aromatase. Not all organs possess the whole steroidogenic pathway, for example, the white adipose tissue expresses only aromatase.

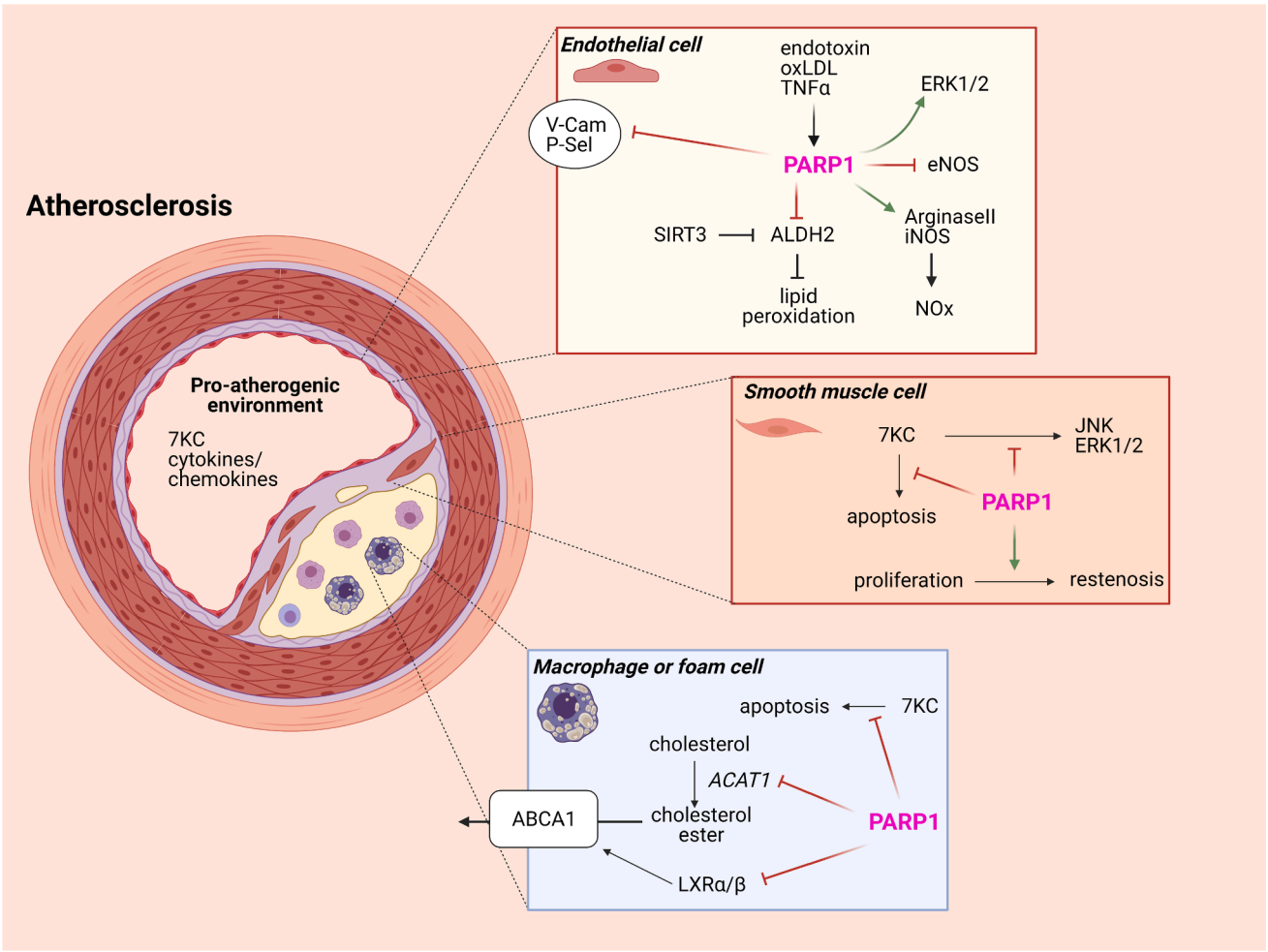

Fig. 6. PARP1-dependent pro-atherogenic pathways elicited by oxidized lipid molecules in atherosclerosis.
Abbreviations: ACAT1 - mitochondrial acyl-coenzyme A/cholesterol acyltransferase-1, ALDH2 – aldehyde dehydrogenase 2, eNOS – endothelial nitrogen oxide synthase, ERK - extracellular signal-regulated kinase, iNOS – inducible nitrogen oxide synthase, JNK – Jun kinase, LXR – liver X receptor, NOx – nitrogen oxides, oxLDL – oxidized LDL, PARP1 – poly(ADP-ribose) polymerase, *P-Sel – P-selectin, TNFα – tumor necrosis factor α,* V-Cam - vascular cell *adhesion* molecule 1 *(CD106),* 7KC – 7-ketocholesterol.

The transport of cholesterol to the mitochondria and the subsequent cleavage of the side chain of cholesterol is a commitment step towards steroid biosynthesis performed. The transport is performed by side chain cleaving enzyme (star) and the cleavage by the enzyme cyp11a1. PARP2 silencing or genetic deletion induces the expression of StAR in murine and cellular models of striated muscles [123]. PARP1 expression showed inverse correlation with the expression of StAR on deltamethrin treatment in the testes of rats [286,287].

The conversion of progesterone to different steroids is a result of the action of a set of cyp enzymes. PARP inhibitors as rucaparib [288], olaparib [289], and veliparib [290] can inhibit a set of cyp enzymes in vitro, hence pharmacological PARP inhibition may interfere with cyp enzyme availability. Conversely, cyp enzymes are responsible for the metabolism of PARP inhibitors, therefore, the availability of cyp enzymes determine PARP inhibitor availability in humans [291]. In murine skeletal muscle, the deletion of PARP2 induces the expression of estradiol 17-beta-dehydrogenase 11 (Hsd17b11), and 5α-reductases (Srd5a1, 2). Srd5a1 and Srd5a2 catalyze the conversion of testosterone to dihydrotestosterone (DHT) [123]. In good agreement with that, muscular DHT levels were higher in the skeletal muscle of PARP2 knockout mice, but systemic DHT levels were left unchanged [123].

Most testosterones can be converted to estrogens by the enzyme aromatase. PARP1 activation was shown to induce the expression of aromatase in fibroblasts derived from breast cancer specimens [292].

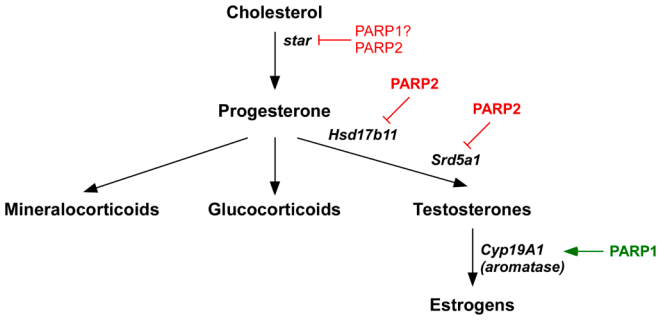

Fig. 7. PARP enzymes interfere with sexual steroid biosynthesis.
The names of the steroid biosynthetic genes that are regulated by PARPs are in italic. The red color marks inhibitory, negative, while the green color marks positive stimulatory effects.
Abbreviations: StAR – steroidogenic acute regulatory protein; Srd5a1 - 5α-reductase; Hsd17b11 - estradiol 17-beta-dehydrogenase 11.

PARP1 activation was dependent on the NAD^+/NADH ratio and NAD^+ availability [292]. Increases in local aromatase expression in breast tumors can support cancer cell growth in estrogen-dependent tumors.

PARylation plays an important role in the function of steroid

hormone receptors and PARPs (PARP1, PARP7) are co-factors of steroid hormone receptors, such as ER [179,195,196], PR [213], AR [180,214–216], and GR [219]. The way PARPs interfere with nuclear receptors is described in Chapter 4. PARP1 activation was implicated in steroid-dependent changes [64,122,154–156,214,293–296]. PARP1 negatively regulates the expression of EPHX1 in hepatocytes that has a role in the formation of diols and through that was shown to be involved in steroidogenesis [258,259].

There is an interplay between estrogens and testosterones in regulating PARP activity. Estrogens were shown to induce oxidative and nitrosative stress and, through that, modulate PARP activity and cell viability in cancer patients and cell models [155,297]. Indeed, estrogens (17-beta-estradiol) activated PARP1 in the peripheral blood mononuclear cells of female mice [155] or MDA-MB-231 breast cancer cells [136] or in a murine model of embryo implantation [163]. Although, the results are circumstantial, lipid-type endocrine disruptors that can mimic estrogens can activate PARP1 in testes or in skin [134,135]. Nevertheless, there are situations when 17-beta-estradiol treatment reduces PARP activation, as in liver [154,155], autoimmune nephritis [156] or in a neuronal cell line (HT22) [158]. Selective ER modulators, raloxifene and tamoxifen can reduce PARP activity in ovariectomized rats [159]. Artificial progestins, medroxyprogesterone and tibolone are activators of PARP2 expression in C2C12 myoblast cells [123]. Among testosterones, DHT was found to induce PARP activity in rat with polycystic ovary syndrome [122], in good agreement with that, castrated males have lower PARP activity [155]. TRPM2 channel expression in the brain was also dependent on the coordinated action of PARP1 and testosterone signaling [294] suggesting that PARP(1) activity and androgen signaling is interconnected.

5.4. *Liver metabolism, toxic injury, AFLD and NAFLD*

Liver harbors a very complex lipid homeostasis, wherein, PARPs have pivotal role by impacting on most branches of hepatic lipid metabolism. Cholesterol metabolism was thoroughly discussed in Chapter 5.2. With regards to fatty acid and triglyceride metabolism under physiological conditions, the induction of SREBP1 in the liver upon the genetic deletion of PARP2 induces fatty acid and triglyceride synthesis [243]. The deletion of PARP2 induced mitochondrial biogenesis through SIRT1 induction and the enhanced expression of PGC-1α PGC-1β, FOXO1, ERRα and PPARα in the liver of PARP2 knockout mice [248]. Gene expression analysis in the liver of PARP2 knockout mice suggests increased mitochondrial fatty acid oxidation due to the higher expression of the aforementioned TFs [248]. In a similar fashion, the deletion of tankyrase in mice induced a set of genes characteristic for triglyceride uptake (LPL, FABP3, CD36) and lipid oxidation (ACO1, CPT1α, MCAD, PGC1α) [100]. In agreement with this, plasma ketone body levels increased in tankyrase knockout mice [100]. The expression of PARP1 is lower in the liver as compared to the testis or the skeletal muscle [91,127,298] and yet little differences were observed between the livers of PARP1 wild type and PARP1 knockout mice kept on chow diet.

In terms of the pathologies of hepatic lipid metabolism, PARPs are promoters of pathological lipid accumulation as non-alcoholic and alcoholic hepatic steatosis (NAFLD and AFLD) and its sequelae. PARP activation has a role in acute toxic injury in the liver inflicted by toxic lipid species that undergo biotransformation for detoxification (e.g. 3-Methylcholanthrene, TCDD or carbon-tetrachloride) [121,132–136,144–149,151–153]. Lipotoxicity is common feature of AFLD and NAFLD (mechanisms of lipotoxicity are discussed in Chapter 3).

NAFLD is a disease with largely unknown etiology, nevertheless, often accompanies obesity and type II diabetes [299]. A fraction of patients advance to NASH, liver fibrosis or hepatocellular carcinoma [299]. Pharmacological inhibition of PARP (olaparib, PJ34 and AIQ) or genetic deletion of PARP1 was protective in numerous models of NAFLD and NASH induced by the high-fat high-sucrose [143], hypercaloric high-fat diet [127,223,248], methionine-choline deficient (MCD) diet [143,223] or high fructose diet (HFRD) [300]. Importantly, PARP inhibition with olaparib not only prevented the development of NAFLD, but was also effective in attenuating the already established pathology, highlighting its clinical potential [143,301]. In contrast, Erener and colleagues [268] found that the deletion of PARP-1 facilitated hepatic lipid accumulation during high-fat diet in mice. The reason for these discrepancies is not clear and could be attributed, at least in part, to differences in PARP-1 knockout mice used in the studies. Interestingly, a recent study has attributed the protective effects of puerarin against NAFLD to attenuation of high-fat diet-induced hepatic PARP-1 expression [302].

The pathogenic role of PARP1 and PARP2 are very similar in AFLD and NAFLD (Fig. 8). NAFLD is characterized by oxidative stress leading to enhanced hepatic PARP1/2 expression and activity [300,303,304]. Consequently, PARP inhibition or the deletion of PARP1 or PARP2 reduced liver damage and liver triglyceride accumulation, fibrosis [223] and inflammation [143,223]. The activation of PARP1 and PARP2 support hepatic lipid accumulation through suppressing mitochondrial oxidation and in particular lipid oxidation [127,143,248,300] through PARylating and inactivating PPARα and limiting SIRT1 activity [127,143,300]. The inhibition of PARP1 attenuates endoplasmatic reticulum stress [143], downregulates de novo lipid biosynthesis [223], while upregulates lipid uptake and lipolysis [300]. An interesting, and to a certain extent relevant observation is that in the induced pluripotent stem cells (iPSCs) differentiated to hepatocytes the overexpression of Oct4/Sox2/Klf4/Parp1 were protective against NAFLD when cells were administered to mice fed on MCD diet [305]. Besides PARP1 and PARP2, TNKS and PARP7 (TiPARP) were also implicated in NAFLD. Tankyrase deletion enhanced expression of LPL, FABP3, CD36, ACO1, CPT1α, MCAD, PGC1α in the liver suggesting enhanced mitochondrial oxidation [100] and in agreement with that, tankyrase inhibition protected against NAFLD in mice [101]. The genetic deletion of PARP7 induced hepatosteatosis in mice [133].

AFLD is also characterized by oxidative and nitrosative stress, DNA damage and PARP activation in the liver upon multiple ethanol feeding regimens (chronic, binge, etc.) [223,306–308]. The molecular mechanism of liver injury and the role of PARP activation in AFLD is similar to NAFLD (Fig. 8). PARP inhibition decreases inflammation and hepatic triglyceride accumulation [223,307]. Inhibition of PARP1 protects

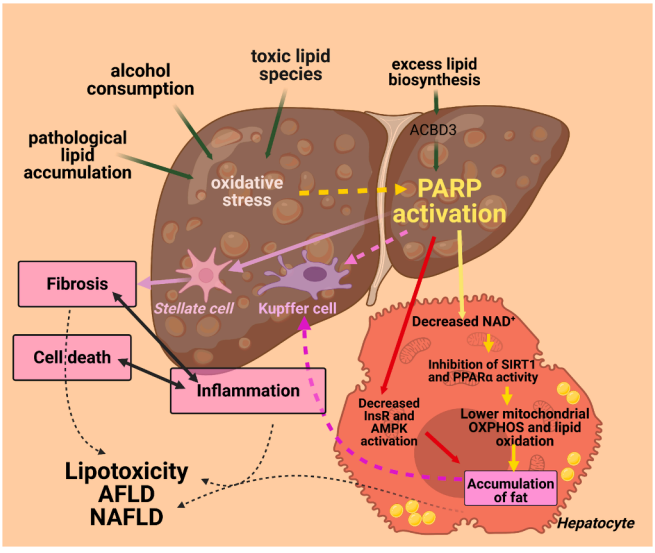

Fig. 8. Molecular pathways of lipotoxicity in NAFLD and AFLD.
Abbreviations: ACBD3 - Acyl-CoA-binding domain containing 3, InsR – insulin receptor, AMPK – AMP-activated protein kinase, PPARα – peroxisome proliferator activated receptor α, OXPHOS – oxidative phosphorylation.

against chronic alcoholic liver injury through inducing the NAD^+-SIRT1 axis [223] and blocking the overexpression of SREBP1, diacylglycerol O-acyltransferase 1 and 2 (DGAT1 and DGAT2), suppressing de novo lipid biosynthesis [223,307]. PPARα expression is suppressed upon alcohol feeding [304,308] that is partially restored upon PARP inhibition [308]. Interestingly, alcohol dehydrogenase is an acceptor of PAR [309].

5.5. Obesity, type II diabetes and energy homeostasis

Below, we discuss PARP-specific contribution of metabolic organs and tissues to the development of obesity and type II diabetes.

5.5.1. White adipose tissue

White adipose tissue (WAT) is a specialized tissue for triglyceride storage, furthermore, it has crucial role in the development of obesity and insulin resistance. Adipocyte differentiation, based on observations from in vitro models, has two phases, clonal expansion and terminal differentiation. A large set of transcription factors play a role in these steps (for review see [113,310]). However, a greater understanding of this process has highlighted the role of various TFs, such as members of the following TF families: C/EBP, NRs, Krüppel-like factor (KLF), signal transducer and activator of transcription (STAT), GATA-binding factors (GATAs), early B cell factor (EBF), and interferon-regulatory factor (IRF) [310,311]. Moreover, regulation of adipogenesis by epigenomic determinants, such as post-translational modifications (PTMs) of histone proteins and the cognate histone-modifying enzymes (e.g., histone methylases and histone deacetylases), have gained attention in recent years [311,312]. From the perspective of PARPs, the C/EBP family and PPARγ have prominent role.

PARP activation was detected during adipocyte differentiation [197,313] (Fig. 9). PARP1 auto-PARylation dominates growth arrest and terminal differentiation phases, nevertheless, other, lower molecular weight bands are also PARylated. In the clonal expansion phase PARP1 can PARylate C/EBPβ on K133, E135, and E139 residues, resulting in decreased binding of C/EBPβ to the promoters of C/EBPα or PPARγ2 and the suppression of adipocyte differentiation [313]. This study explains the suppression of PARP activity in the clonal expansion phase. Furthermore, the compartmentalization of NAD^+ synthesis and compartment-specific regulation of NAD^+ salvage pathways can also regulate adipocyte differentiation. Ryu and colleagues [59] showed that in the clonal expansion phase the expression and activity of nuclear NMNAT-1, a key NAD^+ salvage enzyme, decreases, while NMNAT2 in the cytosol is induced. This swap in the location of NAD^+ biosynthesis suppresses nuclear PARylation that would keep cells undifferentiated and support cytosolic glycolysis [59]. NAD^+ metabolism is a key factor in maintaining the promoter of PPARγ accessible in preadipocytes [210]. The importance of cellular NAD^+ pool and localization [57,314] has been verified in human studies [315].

Also in the clonal expansion phase PARP1 ADP-ribosylates histone H2B on glutamate 35 (H2BE35) and this seems to be a vital chromatin-mediated regulatory event [18]. Interestingly, this glutamate residue is adjacent to a serine residue (serine 36) which is differentially phosphorylated through the course of adipocyte differentiation (maximum levels at around day 2 post-differentiation when PARP1 activity is low) [18]. The ADP-ribosylation of histone H2BE35 prevents phosphorylation on S36, repressing adipogenic gene expression [18]. Modifications on other histones (e.g., H3K27dimethyl) are also modulated by H2BE35 ADP-ribosylation [18].

Schematic diagram illustrating the first and second transcriptional waves in adipogenesis, which are characterized by rapid production and activation of transcription factors, including C/EBPβ, PPARγ, and C/EBPα, as indicated. The levels of PARP1-dependent ADP-ribosylation are also dynamically regulated during adipogenesis. In undifferentiated cells, nuclear NAD^+ and PAR levels are high, but rapidly decrease upon the onset of differentiation. This is reduction in ADP-ribosylation correlates with the changes in NMNAT-1 driven nuclear NAD^+ production

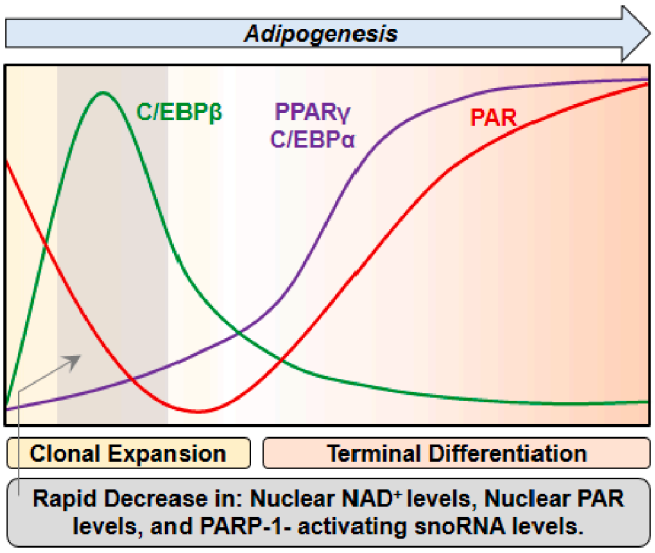

Fig. 9. Dynamic regulation of PARP1-mediated ADP-ribosylation during adipocyte differentiation.

and the levels of PARP1-activating snoRNAs, both of which are critical regulators of PARP1enzymatic activity.

The terminal differentiation phase is characterized by increased PARP1 automodification [197,313]. The group of Michael Hottiger showed that the pharmacological or genetic inhibition of PARP1 reduced the differentiation of 3 T3-L1 preadipocytes by blocking PPARγ activation in the terminal differentiation phase [197,268]. Similar results were shown in an early study by Mark Smulson using 3-amino-benzamide (3AB), an unspecific PARP inhibitor and genetic methods to inhibit PARP1 in 3 T3-L1 cells [7]. PARP1 is necessary for the resolution of topoisomerase II-inflicted double strand breaks upon PPARγ activation and to facilitate the exchange of NCoR-1 (an inhibitory co-factor of PPARγ) to p300 (an activating co-factor of PPARγ) [182,183,196,197].

There is an apparent contradiction between the above-described results, as the inhibition of PARP1 induced the differentiation of 3 T3-L1 cells [59,313], while other authors showed that PARP1 inhibition blocked 3 T3-L1 cell differentiation [7,197,268]. Though there is no clear-cut explanation for this discrepancy; it is possible that different clones of 3 T3-L1 responded differently to PARP inhibition. Since fatty acid biosynthesis equally depends on SREBP1 and on PPARγ, and, as SREBP1 and PPARγ respond differently to PARP inhibition the contribution of the two pathways to fatty acid biosynthesis may be different in different clones.

Other PARP enzymes were also implicated in adipogenesis. Genetic deletion of PARP2 induced lipodystrophy in chow-fed mice, as well as in cellular models [228]. The absence of PARP2 inhibited PPARγ activation and PPARγ-mediated mRNA transcription that was the cause of the dysfunction of adipocytes [228]. Tankyrase expression is the highest in the central nerve system and adipose tissue. Pharmacological tankyrase inhibition decreased abdominal adiposity in mice primarily through inhibiting the PARylation of PGC1α [100,101]. Tankyrases are involved in the regulation of the cell surface export of glucose transporter-4 (Glut4) molecule in adipocytes and fibroblasts [316].

PARP enzymes interfere with multiple processes in adipocytes involving fatty acid uptake, lipid storage, fatty acid biosynthesis, adipokine production and secretion [59,100,183,197,227,228,268,313].

5.5.2. Brown and beige adipocytes

Brown and beige adipocytes are adipocytes specialized in heat generation for which adipocytes are equipped with high levels of mitochondria and fatty acid oxidation machinery [317,318]. These cells are of myogenic origin and it is of note that PARP1 and PARP2 modulate

myoblast differentiation and health [251,319–322], suggesting that PARPs may affect the differentiation of brown and beige adipocytes. Adipose tissue NAD^+ biosynthesis and the subsequent SIRT1 activation is required for mitochondrial biogenesis and energy expenditure [323–325] and PARP activity can modulate NAD^+ availability and SIRT1 activity and through that, PGC1α activation and mitochondrial biogenesis in other cells and tissues [6,23,84,91,248,326].

In good agreement with these, human adipose tissue-derived mesenchymal stem cells (hADMSC) differentiated to white adipocytes responded to PARP inhibition with olaparib by browning associated with enhanced mitochondrial biogenesis and uncoupling protein (UCP)1 induction [327]. This was not associated with the induction of beige molecular markers, suggesting the formation of brown adipocytes. Deletion of PARP1 in mice is characterized by bigger brown adipose tissue size, induction of the expression of UCPs, fatty acid oxidation genes and higher mitochondrial content [91]. In both studies the blockade of PARP activity boosted NAD^+ levels and SIRT1 activity in the brown adipose tissue [91,327]. The genetic deletion of PARP2 does not affect the function of the brown adipose tissue in mice [248]. The pharmacological or genetic inhibition of tankyrases in mice induce energy expenditure [100] in which the browning of the adipose tissue was demonstrated through inhibiting the PARylation of PGC1α [101].

5.5.3. Skeletal muscle

Insulin resistance of skeletal muscle is a key factor in the development of organismal insulin resistance. PARPs regulate lipid oxidation in skeletal muscles. Pharmacological inhibition of PARP or the deletion of PARP1 or PARP2 stimulates mitochondrial lipid oxidation in a SIRT1-dependent fashion in murine and cellular models [91,248,326,328–330]. Pharmacological PARP inhibition or the deletion of PARP2 in mice promotes fatty acid oxidation in skeletal muscle [248,326,328]. Tankyrase inhibition in mice can induce increased energy expenditure through skeletal muscle mitochondrial biogenesis by blocking the PARylation of PGC1α [100,101].

5.5.4. Liver

PARP activation plays a role in liver insulin resistance. Oleic acid treatment of HepG2 cells induced PARP1, while decreased the phosphorylation and, hence, the activity of the insulin receptor (InsR), Akt and GSK3β, AMPK that was reversible by pharmacological inhibition of PARP by PJ34 [140,141]. Decreased phosphorylation of InsR, Akt and GSK3 was dependent on the depletion of NAD^+ and the consequent inhibition of SIRT1 activity and expression [140,141]. In good agreement with this, in a murine model of high-fat high-sucrose diet PARP inhibition protected against NAFLD and the consequent deterioration of glucose homeostasis [143]. The genetic deletion of PARP2 was able to increase mitochondrial biogenesis in the liver in mice through enhancing SIRT1 activity and expression, suggesting a potential role for PARP2 in development of liver insulin resistance [248]. Furthermore, tankyrase inhibition through inducing PGC-1α and, consequently, enhanced mitochondrial activity can protect against liver insulin resistance in mice [101]. PARP7 activation can block hepatic gluconeogenesis [151,152] and facilitate the degradation of PGC-1α that can potentially repress mitochondrial biogenesis in cellular models of hepatocytes and in chicken embryos [151].

5.5.5. Development of obesity, insulin resistance and type II diabetes

Obesity is a multifactorial metabolic disease characterized by excess fat accumulation in the body that leads to adverse health effects. Hereby, we will discuss how the PARP-mediated dysfunction of the metabolic tissues and organs (white adipose tissue, brown adipose tissue, skeletal muscle, and the liver) or the central regulation (central nerve system and the endocrine system) can contribute to development of obesity, insulin resistance and type II diabetes, and diabetic complications. Chronic hyperglycemia associated with diabetes leads to microvascular damage/dysfunction characterized by enhanced oxidative and nitrosative stress and PARP activity [5,278,331–334], which underlies the development of multiple diabetic complications including nephropathy [335], retinopathy [336], cardiomyopathy [333,334], cystopathy [337], lung complications [338] and impaired wound healing [339–341], as was shown in humans, murine and cellular models.

The role of the central metabolic regulation is to facilitate the adaptation of the organism to environmental challenges. To achieve that, the outer and inner sensory information is integrated for the control of metabolic homeostasis to the ventromedial hypothalamus. That region is responsible for sensing the metabolic status of the organism and to elicit adaptive measures, as controlling hunger, satiety and controlling the circadian rhythm of the organism. Whole body deletion of PARP1 disrupts feeding regime and induces the spontaneous locomotor activity in mice [91] highlighting a role for PARP1 in circadian phase entrainment. Circadian changes to PARP1 expression or PARP1 activity was demonstrated in murine models and humans in skeletal muscle, the liver and in immune cells [342–345]. Disrupting the circadian cycle of organisms predisposes to obesity and other metabolic diseases [346–349].

Although, comprehensive studies are missing, PARPs were shown to interfere with hormone expression and secretion as in the case of insulin [4,100,248,350–352], adipokines [100,183,197,228,268], glucagon-like peptide-1 (*GLP-1*) [278] and Insulin-like growth factor (IGF)-1 [353] as demonstrated in cellular, rat and murine models. For interactions with steroid hormones, see Chapters 4.3 and 5.3. The dysregulation of the expression, secretion of these hormones or tissular resistance to these hormones contribute to the development of obesity and its sequelae.

Fat can accumulate when adipocytes are hyperplastic (adipocyte numbers increase) or are hypertrophic (adipocyte size increase). As discussed in Chapter 5.5.1, PARPs are involved in regulating the development and function of adipocytes, hence can interfere with adipocyte hyperplasia and hypertrophy. In obesity the adipose tissue undergoes a low-grade, but persistent inflammation, termed metaflammation that later culminates into fibrosis [354] and the prevention of that tunes the organism towards a “metabolically healthy” obese phenotype [355]. Interestingly, inflammatory signaling can drive adipose tissue browning [356]. As noted earlier in Chapter 2, PARP1 and PARP2 are pro-inflammatory in Th1 and Th2-mediated inflammation [71,72] and studies have found signs of suppressed metaflammation in the WAT upon the deletion of PARP1 [268] or PARP2 [228] in mice. Pharmacological PARP inhibition by INO1001 can suppress inflammatory mediators as IL6 or CRP in humans [73] suggesting that PARP inhibition can suppress metaflammation in obesity.

Obesity can also be a result of pathological changes in energy homeostasis, whereby, cellular mitochondrial activity or physical activity is suppressed [357]. In this context, the genetic deletion of PARP1 or pharmacological PARP inhibition in murine and cellular models enhanced mitochondrial biogenesis and mitochondrial activity in the brown adipose tissue [91,327] and skeletal muscle [91,328,358]. The genetic deletion of PARP2 promoted mitochondrial biogenesis and mitochondrial activity in skeletal muscle and in the liver [248,326] and the genetic deletion of tankyrase increased fatty acid oxidation in skeletal muscle [100,101] and browning of adipose tissue [101]. These changes were accompanied by enhanced spontaneous locomotor activity in PARP1 knockout mice [91]. It is likely that other PARP enzymes, as PARP10, where mitochondrial activation and fatty acid oxidation was reported in cellular models [99], may have similar phenotypic changes. The induction of mitochondrial biogenesis is dependent on NAD^+ sparing and the subsequent activation of SIRT1, PGC1α and AMPK [91,101,248,314,315,328,358,359]. Recent studies [82,83] provided evidence that the deletion of PARP1 induces the diversity of the microbiome in mice that may play role in adipose tissue browning [360,361].

The enhanced mitochondrial function provided protection against hypercaloric high-fat feeding [91,142,183,248,268,328], Western diet

[143] or alleviated obesity caused by the db/db phenotype [101] in mice. Importantly, PARP inhibition is effective both as a pre-treatment or when administered along the high-fat feeding [143,223]. The elimination of fatty acids from the circulation ameliorates insulin resistance [362], therefore, increased fatty acid oxidation and the subsequently lower serum fatty acid content may contribute to the beneficial metabolic effects of PARP inhibition [101,248]. Importantly, a reduction in adipose tissue PARP activity is linked to weight loss in humans [359]. While in obesity in humans the opposite occurs, PARP activity increases and NAD^+ levels and SIRT1 activity decreases [315] suggesting that the observations in mice can be translated to human obesity.

A consequence of obesity is insulin resistance that characterizes type II diabetes. Pharmacological or genetic inhibition of PARP1 improved the performance of mice on oral glucose tolerance tests and improved insulin sensitivity [91,143,328] most likely as a result of improved skeletal muscle mitochondrial function [91,328]. The frequency of type II diabetes is lower in human individuals homozygous for the SNP rs1136410 that confers lower PARP activity as compared to wild type homozygotes or heterozygotes [265], supporting an important role of PARP1 in human diabetes mellitus. It is of note that PARP1 inhibition is protective against beta cell death in murine models of type I diabetes [2–4] and controls other functions in beta cells, such as insulin gene and protein expression as demonstrated in Ins-1 cells [351]. Genetic or pharmacological inhibition of tankyrase leads to enhanced mitochondrial biogenesis and function alongside with better insulin sensitivity in murine models [100,101]. Apparently, improved skeletal muscle and probably liver mitochondrial activity is responsible for better insulin sensitivity [100,101]. The deletion of PARP2 in mice, while protects against diet-induced obesity and improves insulin sensitivity and glucose clearance, on high-fat feeding the loss of PARP2 deteriorates the proliferative response of beta cells to increasing insulin need and, hence, blunts insulin release and glucose tolerance [248].

In contrast to these observations a study by Devalaraja-Narashimha and Padanilam [363] found that PARP1 knockout mice fed on high-fat diet became more obese compared to wild type littermates and had worsened diet induced diabetes. Another study from the laboratory of Michael Hottiger found a similar worsening of diabesity in PARP1 knockout mice [268]. Yet, there is no clear-cut explanation for these discrepancies, the conflicting studies were performed on two different PARP1 knockout strains, one generated by Zhao-Qi Wang [298] and later deposited at Jackson Laboratories (Bar Harbor, Maine, USA) on an SV129 background; the other strain was generated in the laboratory of Gilbert de Murcia [364] on a C57/Bl6J background. In fact, the metabolic behavior of the two backgrounds are profoundly different [365,366] that may provide a reasonable explanation for the controversy. A solution to resolve these issues would be the use of a transgenic PARP1loxP mouse strain (deposited at JAX) that can help in overcoming background issues and may resolve the yet unstudied organ-organ interactions. Notable, most metabolic/diabetes related studies performed in PARP1 knockout mice on C57/Bl6J were also confirmed with the use of numerous structurally distinct PARP inhibitors [62,63,65].

5.6. Other pathologies with PARP-mediated changes to lipid metabolism

In the central nervous system docosahexaenoic acid is protective against binge alcohol drinking-induced murine models of neuroinflammation [157,158,367]. 7-ketocholesterol induces neuroinflammation and demyelination through PARP1 activation in mice [8]. TLR2 is a driver of neuroinflammation and can be activated by multiple ligands, such as bacterial lipopolysaccharide (LPS) or 15alpha-hydroxicholestene. TLR2 activation in mice leads to oxidative stress and PARP activation which were implicated in the pathomechanism of experimental autoimmune encephalomyelitis, a model for multiple sclerosis [115] and in the deterioration of object recognition [368]. The response to ischemia-reperfusion injury in the brain of mice was dependent on testosterone-dependent activation of transient receptor potential M2 (TRPM2) ion channel [294].

In the heart PARP1/2 activation contributes to a multitude of pathologies [62,63,65,276]. Lipid molecules can inhibit PARP1/2 and alleviate cardiac pathologies, as 25-hydroxycholesterol in ischemia-reperfusion injury [116] or lipoic acid [130] in cardiac hypertrophy in mice. The response of rat cardiomyocytes and cardiac fibroblasts to lipid species through nuclear receptors is modulated by PARP1 [227].

PARP1 interferes with the lipid metabolism of the skin at multiple points. PARP1 controls the expression of a fatty acid transporter, fatty acid binding protein 7 (FABP7) in keratinocytes [249], whereby PARP1 regulates the available polyunsaturated fatty acids in skin [249]. Through that, PARP1 may interfere with skin barrier function and the production of lipid inflammatory mediators [249] in the oxazolone-induced contact hypersensitivity murine model of skin inflammation. PARP2 was not involved in oxazolone-induced contact hypersensitivity or in irritative dermatitis [369] suggesting a selectivity in that regard for PARP1 enzyme.

UVB irradiation induces mitochondrial biogenesis and lipophagy in keratinocytes, most likely to support the energetic needs of DNA repair [250]. Upon UVB irradiation PARP1 facilitates the repair of cyclobutane-pyrimidine dimers [370,371]. Cyclobutane-pyrimidine dimers initiate a yet unknown signaling pathway that upregulates mitochondrial biogenesis, lipophagy and fatty acid oxidation, rendering keratinocytes hypermetabolic [371]. PARP inhibition accentuates the hypermetabolic rearrangement of keratinocytes [250]. This pathway is key for keratinocyte survival upon UVB-induced DNA damage and to control UVB-induced keratinocyte differentiation. Similar to these observations, in another model system, DNA repair-deficient ($Csa^{-/-}|Xpa^{-/-}$ mouse) models were irradiated with UVC. UVC induced mitochondrial oxidation and, in particular, fatty acid oxidation in a PARP1-dependent fashion; loss of PARP1 diminishes the induction of the fatty acid oxidation [255].

Circumstantial evidence point towards the involvement of PARP1 overactivation in bile acid-induced nephrotoxicity in cholestasis in rats [120].

Aging comes along with a gradual deterioration of mitochondrial function and an increasing incidence of metabolic diseases. Aging is associated with higher PARP activity [372,373] that consequently impacts on the SIRT1-NAD^+-PARP1 balance [374–380] leading to mitochondrial dysfunction as demonstrated in humans and in murine models. Consistently with this, chronic inhibition of PARP in aging rats improves endothelial function and cardiac bioenergetics and function [381–383] without any adverse effects. In a very elegant set of experiments, Mangerich and colleagues [384] demonstrated that the overexpression of PARP1 in mice while protected against DNA damage-associated neoplasias, it increased the incidence of (lipid)metabolic diseases. PARP1-mediated damage to fatty acid metabolism was highlighted in studies on Cockayne syndrome-associated factors in mice [255,385]. We refer readers to reviews on the multi-pronged connections between PARPs and aging: [275,386–389].

6. Conclusion and perspective

PARPs are involved in regulating lipid metabolism at multiple steps, being involved in multiple pathologies connected to lipid metabolism (Fig. 10). The connections between PARPs and lipid metabolism are bidirectional, the activity of PARPs are regulated by multiple lipid species, involving drugs, while PARP enzymes regulate lipid metabolism and are involved in the pathogenesis of several lipid metabolism-related disorders.

Although, the majority of data point towards the metabolic disruptor role of PARPs, there are multiple contradictions that are yet unexplained. In terms of HDL/LDL ratios [262,265] vs. [268], adipose tissue differentiation (reviewed in [113]), hepatosteatosis [268] vs. [127,143,211,223,302,329], obesity and energy homeostasis [363] vs. [91]).

The pathobiology of the diseases discussed in the review is complex and the pathways involved in the pathogenesis are multi-pronged. PARP inhibition has a very potent protective effect on the vasculature, namely, on the microvasculature [23,63,65,85,274]. Most pathologies discussed in the review have an inflammatory component that is efficiently suppressed by PARP inhibition. Importantly, inflammation in the liver and adipose tissue promotes metabolic dysregulation, enhanced oxidative/nitrative stress-PARP pathway, increased lipid deposition, and fibrotic remodeling associated with microcirculatory dysfunction; and all these processes are closely interrelated [303]. Finally, PARP inhibition can prevent necrosis or divert necrosis to apoptosis [86,87,107–110] that has strong beneficial effects. These effects should be considered alongside the direct lipid-elicited effects.

On a wider perspective, the PARylation machinery on the top of PARPs, the "writers" includes "erasers" and "readers". These enzymes are important in NAD^+ metabolism [390] similar to PARPs. Connections between the erasers and writers and (lipid) metabolism is ill-characterized. PARG inhibition or deletion often mimics the effects of pharmacological PARP inhibition [391–394], involving features pointing towards a possible involvement in lipid metabolism. PARG can be found in the mitochondrial matrix [103,395] and is involved in regulating mitochondrial function [396–398] suggesting its involvement in regulating OXPHOS. Furthermore, PARG is involved in regulating features involved in the development of atherosclerosis [399,400] and plays role in androgen signaling [401] suggesting that PARG may have a similarly widespread connection with (lipid) metabolism as PARP1 or PARP2. ARH3 is responsible for removing ADP-ribose units in the mitochondrial matrix [402,403]. The loss of other readers and erasers as MACROD1 or TARG1 leads to disruption of mitochondrial or nucleolar morphology [404]. The involvement of ARH3, MACROD1 or TARG1 in mitochondrial function suggests that these factors can be involved in the regulation of lipid oxidation and other lipid metabolism-related mitochondrial features. PARPs are linked to other NAD^+-dependent enzymes and processes that can be considered as a warehouse of indirect effects [57,93,95,405].

There are several interesting areas that require further exploratory studies on the involvement of PARPs from the perspective of metabolism, such as cancer cachexia [322,406–408], biological clocks [91,342–345] or hormonal regulation [3,100,123,183,197,228,248,268,351,353]. The diseases we reviewed in this synopsis affect large population and often have very limited therapeutic options (e.g. NAFLD/NASH and AFLD [299]). Increasing preclinical and clinical evidence coupled with availability of clinically approved PARP inhibitors supports the need for translational human studies on the applicability of PARP inhibitors in lipid metabolism-related diseases [63,65,73,265,315,359].

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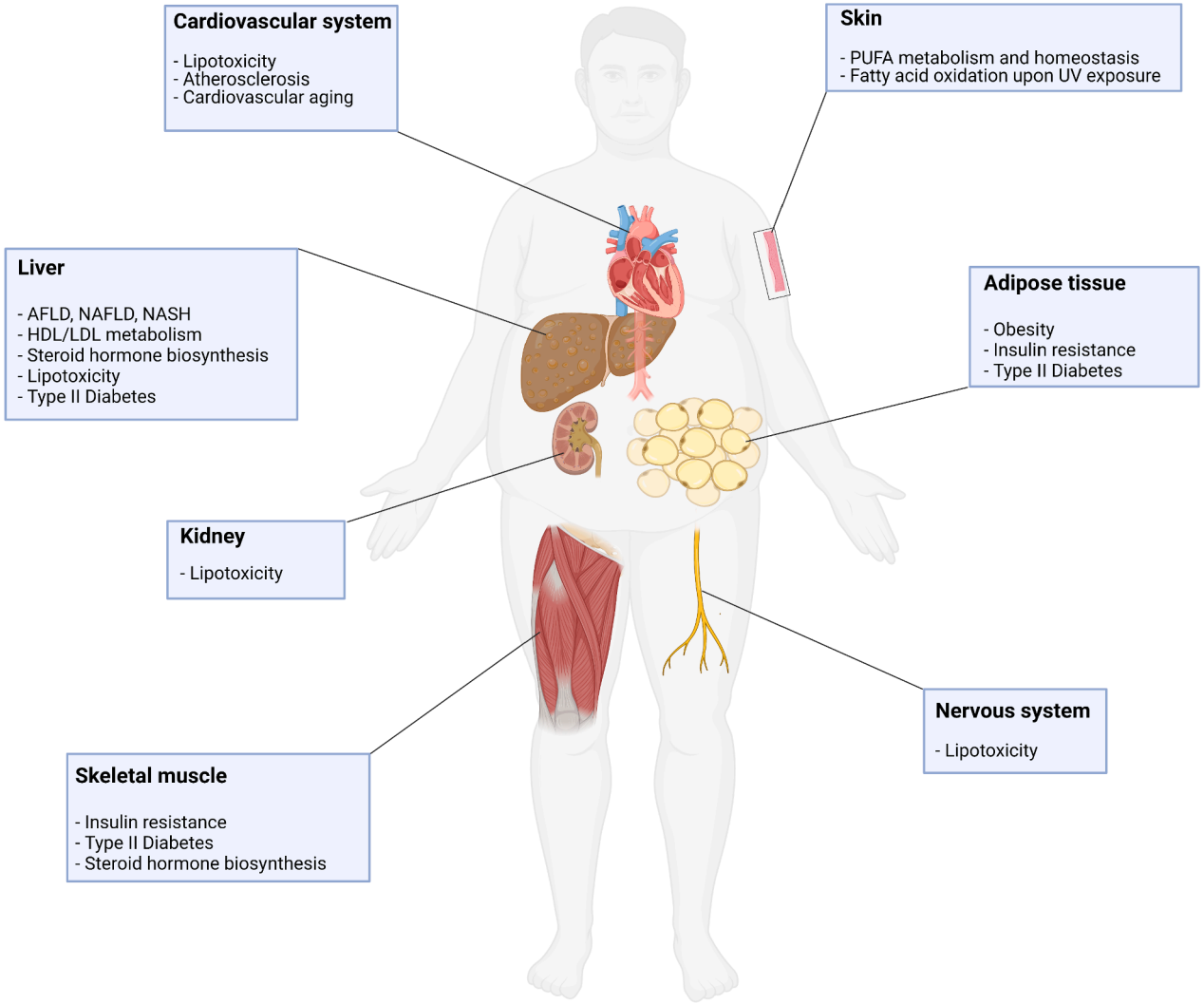

Fig. 10. An overview of the PARP-mediated pathologies of lipid metabolism.

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Patents

U.S. Patent 9,599,606 (W. L. Kraus and B. A. Gibson) covers a set of ADP-ribose detection reagents, which have been licensed to and are sold by EMD Millipore. U.S. Patent 9,926,340 (W. L. Kraus, B. A. Gibson et al.) covers a set of clickable NAD^+ analogs and analog sensitive PARP mutants that allow PARP-specific ADP-ribosylation of proteins. U.S. Patent US20140065099A1 covers methods to improve metabolic health through inducing cellular NAD^+ content.

Author contributions

PB conceptualized the manuscript. All authors were involved in writing the original draft, in revision and editing, as well as, in visualization.

Declaration of Competing Interest

W.L.K. is a founder and consultant for Ribon Therapeutics, Inc. He is a coholder of U.S. Patent 9,599,606 covering a set of ADP-ribose detection reagents, which have been licensed to and are sold by EMD Millipore. He is also a coholder of U.S. Patent 9,926,340 covering a set of clickable NAD^+ analogs and analog sensitive PARP mutants. PB is a coholder of U.S. Patent US20140065099A1 covering methods to increase cellular NAD^+ levels and improve metabolic health. Other authors declare no conflict of interest.

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