SPECIAL SECTION: REVIEW

The role of ADP-ribose metabolism in metabolic regulation, adipose tissue differentiation, and metabolism

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Poly(ADP-ribose) polymerases (PARPs or ARTDs), originally described as DNA repair factors, have metabolic regulatory roles. PARP1, PARP2, PARP7, PARP10, and PARP14 regulate central and peripheral carbohydrate and lipid metabolism and often channel pathological disruptive metabolic signals. PARP1 and PARP2 are crucial for adipocyte differentiation, including the commitment toward white, brown, or beige adipose tissue lineages, as well as the regulation of lipid accumulation. Through regulating adipocyte function and organismal energy balance, PARPs play a role in obesity and the consequences of obesity. These findings can be translated into humans, as evidenced by studies on identical twins and SNPs affecting PARP activity.

Brief introduction to ADP-ribose metabolism

The field of poly(ADP-ribose) polymerases (PARPs or ARTDs) has come a long way since the discovery of a nuclear poly(ADP-ribosyl)ating (PARylating) enzyme in 1963 (Chambon et al. 1963). PARPs now constitute a superfamily of at least 17 members in human that share a conserved catalytic domain (Amé et al. 2004; Hottiger et al. 2010). ADP-ribosylation is a posttranslational modification, during which the ADP-ribosylation enzymes cleave NAD^+ and attach the resulting ADP-ribose (ADPR) units to acceptor proteins. ADP-ribosylation is referred to as mono(ADP-ribosyl)ation (MARylation), oligo (ADP-ribosyl)ation, or poly(ADP-ribosyl)ation (PARylation), based on the number of the ADPR units added to the acceptor protein (Amé et al. 2004; Hottiger et al. 2010). Although all PARPs inherited the family name of the founding member, PARP-1, the PARP "polyenzymes" include only PARP-1, PARP-2, and the tankyrases (PARP-5a and PARP-5b) (Gibson and Kraus 2012). Other members perform only MARylation or oligo(ADP-ribosyl) ation, while PARP13 possesses no enzymatic activity (Hottiger et al. 2010). To our current understanding, the majority of PARP activity is attributed to PARP1 (80%–85%), while the rest is largely attributed to PARP2 (Amé et al. 1999; Schreiber et al. 2002; Szanto et al. 2011). In most cases, the major acceptor of PAR is PARP1 itself (termed auto-PARylation); nevertheless, with the use of state-of-the-art proteomics a large set of PARylated or ADP-ribosylated proteins were identified and this process is termed trans-PARylation (Chapman et al. 2013; Gibson et al. 2016; Abplanalp et al. 2018; Leslie Pedrioli et al. 2018; Palazzo et al. 2018) (for a comprehensive database of ADP-ribosylated proteins see Vivelo et al. (2017).

ADP-ribose unit(s) have rapid turnover and are removed by isoforms of poly(ADP-ribose) glycohydrolase (PARG) (O'Sullivan et al. 2019; Slade 2020), ADP-ribosyl hydrolase 3 (ARH3) (Oka et al. 2006; Rack et al. 2020), and ADP-ribosyl protein lyase (Kawaichi et al. 1983). PAR polymers can be recognized by a set of proteins that consequently localize to sites marked by PARP enzymes (Barkauskaite et al. 2013; Feijs et al. 2013). Karlberg et al. (2013) classified enzymes involved in ADPR metabolism and recognition as writers, readers, and erasers.

PARP1, PARP2, and PARP3 can be activated by DNA strand breaks and aberrant DNA forms (Menissier-de Murcia et al. 1989; Gradwohl et al. 1990; Kutuzov et al. 2013, 2015). Recently, other regulatory routes were described. PARP2 is activated by RNA forms (Léger et al. 2014); numerous signal transduction pathways, or the stability of PARP proteins were shown to modify the activity of PARP isoforms (Gagné et al. 2009; Cantó et al. 2013). PARPs, especially PARP1 and PARP2, are major NAD^+ consumers in the cell (Bai et al. 2011a,b; Mohamed

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et al. 2014) and play a crucial role in regulating NAD^+ availability and the nonredox functions of NAD^+ (often referred to as the NAD^+ node) (Houtkooper et al. 2010). On the other hand, PARP activity is dependent on NAD^+ levels in cellular compartments and requires a continuous supply of NAD^+. Nicotinamide mononucleotide adenylyl transferase (NMNAT) -1, -2, and -3 are NAD^+ synthase enzymes that produce NAD^+ from nicotinamide mononucleotide and ATP (Chiarugi et al. 2012; Cohen 2020). Thus, NMNATs can "feed" PARPs with their substrate and modulate PARP catalytic activity (Berger et al. 2007; Zhang et al. 2012; Ryu et al. 2018). There are pharmacological inhibitors available for the study of PARP biology, as well as for clinical use. Clinically available PARP inhibitors include ABT-888 (Veliparib from Abbott/Abbvie) rucaparib (Rubraca from Agouron/Pfizer/Clovis), talazoparib (Talzenna from Lead/Biomarin/Medivation/Pfizer), olaparib (Lynparza from KuDos Pharmaceuticals/AstraZeneca+Merck), and niraparib (Zejula from Merck/Tesaro/GSK) (for detailed review, see Slade 2020; Curtin and Szabo 2013). Although, none of the current PARP inhibitors seem to discriminate between PARP enzymes (Wahlberg et al. 2012), enzyme-specific inhibition of mono-PARP enzymes may be possible (Venkannagari et al. 2016; Upton et al. 2017; Holechek et al. 2018).

PARP enzymes have widespread biological functions ranging from DNA repair and chromatin structure (Javle and Curtin 2011; De Vos et al. 2012; Dantzer and Santoro 2013), RNA transcription, protein translation, and degradation (Kraus and Hottiger 2013; Bai 2015), cell division, tumor biology (Curtin and Szabo 2013), immune processes (Fehr et al. 2020) metabolism, and mitochondrial biology (Bai and Cantó 2012; Bai et al. 2015), oxidative stress biology, and cell death and differentiation, and aging (Mangerich et al. 2010; Burkle and Virag 2013; Fatokun et al. 2014). In this review, we focus on the metabolic properties of PARP enzymes.

PARP enzymes in metabolism

PARP enzymes impact metabolism at multiple points, exerting regulatory functions on higher order organismal and basic cellular processes. From another perspective, PARPs impact both central and peripheral metabolic regulation. Frequently, PARP activation represent pathological disruptive metabolic signals. Here, we briefly review PARP-mediated pathways in metabolic regulation. Metabolic pathologies associated with PARP activation are listed in Table 1.

PARPs in regulating central and peripheral organismal metabolic homeostasis

PARP enzymes are widely expressed in almost all tissues and cells of the human organism, including metabolic tissues and organs, such as the liver, skeletal muscle, hormone glands, adipose tissue (white, brown, and beige), and the nerve system (Bai 2015). Central metabolic regulation encompasses the coordinated regulatory activity of the central nervous system and the hormonal system, which allows the organism to adjust to environmental and internal metabolic challenges. Such signals are integrated into the nuclei of the ventromedial hypothalamus, which serve as a central orchestrator and *zeitgeber* for other organs through hypothalamic neurohormonal changes (Cedernaes et al. 2019). Whole body genetic deletion of *PARP1* alters feeding entrainment in mice and changes spontaneous locomotor activity (Bai et al. 2011b), suggesting a role for PARP1 in the circadian phase of entrainment. PARP1 expression and PARP1 activity show circadian changes in murine models and humans that contribute to circadian entrainment of transcriptional programs in skeletal muscle, the liver, and in the cells of the immune system (Mocchegiani et al. 2003, 2004; Asher et al. 2010; Zhao et al. 2015). PARP1 can achieve circadian regulation of gene transcription through the following actions: (1) interacting with 11-zinc-finger protein or CCCTC-binding factor (CTCF) and converting parts of the chromatin to heterochromatin in a time-dependent fashion (Zhao et al. 2015) and (2) interacting with and ADP-ribosylating Clock protein (Asher et al. 2010). Yet-uncovered pathways may also be active. PARP1 activation seems to be vital for sensing or mediating NAD^+/NADH levels to be integrated into cellular energy sensing and signaling. Although, the aforementioned pathways were described in nonneuronal models, PARPs are abundantly expressed and active in the nervous system (Komjati et al. 2004; Fatokun et al. 2014) and feeding and locomotion behavior changes in the *PARP1* knockout mice (Bai et al. 2011b), making it likely that these processes are active in neurons and other cellular elements of the nervous system. It is important to note that disrupting circadian entrainment increases the risk for obesity and the consequences of obesity (Kettner et al. 2015); however, this has not been studied in the context of PARP activation.

PARPs interfere with hormonal signaling at various points. PARPs regulate hormone levels, including intramuscular androgen production (Marton et al. 2018b). Fasting serum insulin levels were lower in *PARP2* knockout mice (Bai et al. 2011a), weak PARP inhibitors were shown to restore insulin expression (Ye et al. 2006) and the deletion of Tankyrase 1 (*PARP5a*, *TNK1*) induced serum insulin levels (Yeh et al. 2009). Pharmacological inhibition or genetic deletion of PARP1 protects against streptozotocin-induced β-cell death that impairs insulin production (Burkart et al. 1999). Interestingly, the deletion of *PARP2* impairs β-cell function and proliferation through blocking *pdx-1* (Bai et al. 2011a). PARP1 and PARP2 were shown to modulate adipokine expression (Bai et al. 2007; Yeh et al. 2009; Erener et al. 2012a,b; Lehmann et al. 2015).

The sensing of hormones is also regulated by PARPs. Nuclear hormone receptors use PARPs as cofactors (Table 2). Therefore, nuclear hormone receptor activation is PARP-dependent. Insulin-like growth factor (IGF)-1 signaling is potentiated by PARP inhibition (Amin et al. 2015). Furthermore, PARP1 interferes with GLP-1 signaling that may interfere with insulin secretion from β cells (Liu et al. 2011). PARP1 and PARP2 activation were

Table 1. *PARP-mediated metabolic diseases*

Disease/condition	PARP(s) involved	Phenotype	Model/source of evidence	References
Obesity	PARP1, PARP2	Down-regulation of NAD^+/sirtuin pathway is related to obesity; the absence of PARP1 or PARP2 protects against diet-induced obesity	Monozygous twin study, *PARP1* knockout mice, *PARP2* knockout mice, PARPi	Bai et al. 2011a,b; Jukarainen et al. 2016; Rappou et al. 2016
		Impaired PPARγ activation and lipid accumulation upon PARP1 or PARP2 silencing.	*PARP2* knockout mice, *PARP1* and *PARP2* silencing, PARPi	Bai et al. 2007; Erener et al. 2012a; Lehmann et al. 2015
	PARP1	The absence of PARP1 or PARP2 exacerbates diet-induced obesity	*PARP1* knockout mice	Devalaraja-Narashimha and Padanilam 2010
Hyperlipidemia	PARP1	An SNP that reduces PARP activity correlates with higher HDL levels	Population study	Wang et al. 2017
		Knockout of *PARP1* decreases serum TG and FFA levels.	*PARP1* knockout mice	Bai et al. 2011b
		Serum cholesterol levels increase upon PARP inhibition	PARPi	Erener et al. 2012b
Hypercholesterolemia	PARP2	In *PARP2* knockout mice serum HDL levels decrease, while LDL levels remain unchanged	*PARP2* knockout mice	Szántó et al. 2014
Type II diabetes	PARP1	Serum cholesterol levels increase upon PARP inhibition	PARPi	Erener et al. 2012b
	PARP1	Genetic deletion of *PARP1* exacerbates high fat feeding-induced type II diabetes	*PARP1* knockout mice	Devalaraja-Narashimha and Padanilam 2010; Erener et al. 2012b
Diabetic sequels	PARP1	*PARP1* deletion or PARPi treatment protect against diabetic (micro)vascular dysfunction	*PARP1* knockout mice, PARPi	Soriano et al. 2001; Pacher and Szabo 2005, 2006
	Not specified	PARP inhibition promotes wound healing and angiogenesis at ischemic wounds in diabetes	PARPi, patient samples	El-Hamoly et al. 2014; Zhou et al. 2017; Bodnár et al. 2018
	Not specified	PARP inhibition ameliorates development of diabetic nephropathy	Type 2 diabetes *db/db* mouse model, PARPi	Szabo et al. 2006
	PARP1	PARP1 inhibition protect against diabetic oculopathy	Murine type 2 diabetes models, PARPi	Szabo 2005
AFLD	PARP -1	PARP1 inhibition protects against alcohol-induced steatosis and steatohepatitis	Alcohol-fed mouse model, *PARP1* knockout mice, PARPi	Zhang et al. 2016; Mukhopadhyay et al. 2017; Huang et al. 2018
NAFLD	PARP1, PARP2	Genetic deletion of *PARP1* or *PARP2* or PARP inhibition protects against diet-induced hepatic lipid accumulation	High-fat feeding-induced steatosis, MCD-deficient model, *PARP1* knockout mice, *PARP2* knockout mice, PARPi	Bai et al. 2011a; Gariani et al. 2017; Mukhopadhyay et al. 2017; Huang et al. 2018
	PARP1	Genetic deletion of *PARP1* leads to hepatic lipid accumulation	*PARP1* knockout mice	Erener et al. 2012b
Toxic steatohepatitis	PARP-7	Absence of PARP7 (TiPARP) results in increased AHR activity due to reduced mono-ADP-ribosylation leading to increased dioxin sensitivity	*PARP7* knockout mouse model	Hutin et al. 2018
PCOS	PARP1	Negative correlation between PARP activity and PCOS related metabolic disorders	Wistar rat model	Masszi et al. 2013

Continued

Table 1. *Continued*

Disease/condition	PARP(s) involved	Phenotype	Model/source of evidence	References
Atherosclerosis	PARP1	Genetic deletion of *PARP1* or PARP inhibition alleviates plaque formation, lipid deposition and inflammation in atherosclerotic plaques	*PARP1* knockout mice, PARPi	Martinet et al. 2002; Kiss et al. 2006; Oumouna et al. 2006; Oumouna-Benachour et al. 2007; Ambrose et al. 2009; Liu et al. 2011; Sunderland et al. 2011; Shen et al. 2012; Wei et al. 2013; Xu et al. 2014; Shrestha et al. 2016
Cancer cachexia	PARP1, PARP2	*PARP1* and *PARP2* deletion counterbalances down-regulation of muscle-specific microRNAs, ultimately leading to improvements in body and muscle weights of cachectic animals	*PARP1* knockout mice, *PARP2* knockout mice	Chacon-Cabrera et al. 2015
Hashimoto thyroiditis	PARP1	Association only, speculated connection between PARP1 variants and PARP1 regulated inflammatory response gene expressions	Human patient study	Koc et al. 2014
Aging	PARP1	Lower PARP1 expression improves aging-related metabolic pathologies, while increasing risk for neoplasia	*PARP1* knock-in mice	Mangerich et al. 2010
	PARP1	Higher PARP activity improves life span	Population studies	Muiras et al. 1998

(PARPi) PARP inhibitor; (TG) triglyceride; (FFA) free fatty acid; (AFLD) alcoholic fatty liver disease; (NAFLD) nonalcoholic fatty liver disease; (PCOS) polycystic ovary syndrome.

shown to be a key step in the development of insulin resistance (for review, see Bai and Cantó 2012).

Hormones, such as insulin (Horvath et al. 2008), estrogens (Mabley et al. 2005; Jog and Caricchio 2013; Joshi et al. 2014), androgens (Shimizu et al. 2013), progesterone (Ghabreau et al. 2004), artificial steroids, and vitamin D (Marton et al. 2018b) can modulate the expression and activity of PARP1 and PARP2. Endocrine disruptors were also shown to modulate PARP activity (Chen et al. 2013; Guerriero et al. 2018). These observations suggest feedback loops where PARPs interfere with hormonal signaling and hormones regulate PARP availability and activity.

PARPs interplay with energy sensor systems in cells (for review, see Bai et al. 2015). These systems assess the energy charge of cells (NAD^+/NADH or ATP/(ADP + AMP) ratio) and the availability of nutrients (amino acids, oxygen, etc.) and shape cellular metabolism to meet these challenges.

PARPs in carbohydrate metabolism

PARPs regulate points in glycolysis (Hopp et al. 2019), the core pathway of glucose catabolism. PARP1 activation hampers glycolytic flux, inducing metabolic dysfunction (Ying et al. 2002, 2003; Devalaraja-Narashimha and Padanilam 2009; Módis et al. 2012; Robaszkiewicz et al. 2014). Tankyrase 1 and Tankyrase 2 (TNK1, TNK2) regulate glucose transporter 4 (Glut4) translocation to the cytoplasmic surface in an ADP-ribosylation-dependent manner and, thus play a vital role in regulating glucose (and glutamine) availability and glycolytic flux (Yeh et al. 2007). The next step in glucose catabolism is the phosphorylation of glucose by hexokinase to form glucose-6-phosphate, which represents a commitment to glycolysis. Hexokinase is localized to the mitochondrial surface to help synchronize glycolytic flux and mitochondrial oxidation (Andrabi et al. 2014). PARP1 activation disrupts this synchronized function, reducing glycolytic influx (Andrabi et al. 2014; Fouquerel et al. 2014). This observation is further underlined by the observation that the supplementation of pyruvate, the end product of glycolysis, can alleviate cellular dysfunction and cell death upon PARP1 activation (Ying et al. 2002, 2003; Suh et al. 2005; Zeng et al. 2007). In agreement with these observations, the down-regulation of PARP1 supports glycolysis (Regdon et al. 2019). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is an NAD^+-dependent enzyme in glycolysis. PARP1 can PARylate and hence inhibit GAPDH (Du et al. 2003). Furthermore, since GAPDH is NAD^+-dependent, NAD^+ breakdown by cytoplasmic PARPs can limit

Table 2. *Known PARP-interacting nuclear receptors*

Nuclear receptor	PARP partner	Effects	References
ER	PARP1/-2	PARP1 is a positive regulator of ER.	Zhang et al. 2013
		PARP1 is required to reseal topoisomerase IIβ-induced DNA breaks associated with ER activation	Ju et al. 2006
		Estrogen is capable of counteracting PARP activation with an unknown mechanism	Mabley et al. 2005; Zaremba et al. 2011
		PARP2 does not interfere with ERβ	Bai et al. 2007
		PARP2 is a positive regulator of ERα	Szántó et al. 2012
PR	PARP1	Progesterone stimulates PARP1; PR interacts with PARP1	Ghabreau et al. 2004
RAR	PARP1	PARP1 is a positive cofactor of RAR	Pavri et al. 2005
TR	PARP1	PARP1 is a positive cofactor of TR; PARP1 is necessary for the activity of TR/RXR heterodimer, while its overexpression hampers nuclear receptor transactivation	Miyamoto et al. 1999
RXR/PPARα	PARP1	PARP1 PARylates and inactivates PPARα	Huang et al. 2017
RXR/PPARγ	PARP1/-2	PARP2 is a positive cofactor of the RXR/PPARγ heterodimer binding to PPARγ-mediated promoters.	Bai et al. 2007
		PARP1 is necessary for normal expression of PPARγ-mediated genes in adipocytes	Erener et al. 2012a
		PARP1 overactivation hampers adiponectin expression by PARylating PPARγ	Huang et al. 2009
		PARP1 is required for PPARγ cofactor exchange.	Lehmann et al. 2015
NOR1, Nurr1	PARP1	PARP1 is a cofactor of NOR-1 and Nur-1 transcription; PARP1 overexpression represses NOR-1 and Nur-1 transcription	Ohkura et al. 2008
AR	PARP1, PARP2	PARP1 is a positive regulator of the AR promoter; PARP1 and PARP2 are positive cofactors of AR	Shi et al. 2008; Schiewer et al. 2012; Gui et al. 2019
LXR	PARP1	PARP1 represses ABCA1 expression and cholesterol efflux in macrophages	Shrestha et al. 2016
LXR	PARP-7	PARP-7 coregulates (activates) LXR through ADP-ribosylation	Bindesboll et al. 2016
GR	PARP1	PARP1 and GR are interacting partners	Muthumani et al. 2006

(ER) Estrogen receptor; (PR) progesterone receptor; (RAR) retinoic acid receptor; (TR) thyroid hormone receptor; (RXR) retinoid X receptor; (PPAR) peroxisome proliferator activated receptor; (NOR1) neuron-derived orphan receptor 1; (AR) androgen receptor; (LXR) liver X receptor; (GR) glucocorticoid receptor.

GAPDH activity and, consequently, glycolytic flux (Hopp et al. 2019). These results were confirmed by the observation that *PARP1* knockout mice have higher respiratory quotient, suggesting a shift toward glucose oxidation (Bai et al. 2011b). Although pyruvate dehydrogenase complex is not considered as a member of the glycolytic enzymatic machinery, it is important to note that three subunits of the complex (PDPR, PDHA1, and PDHX) are subject to poly-ADP-ribosylation, which may regulate the fate of pyruvate, whether it can enter the TCA cycle, convert to lactate, or undergo gluconeogenesis (Hopp et al. 2019).

PARP10 and PARP14 are two poorly characterized members of the PARP family. Nevertheless, they seem to be connected to carbohydrate metabolism. Silencing of PARP10 induces glycolysis and mitochondrial oxidation, rendering cells hypermetabolic (Márton et al. 2018a). PARP14 can support glycolysis in lymphoma cells, although the molecular mechanism has not been elucidated (Cho et al. 2011). Another interesting feature of PARP14 is its physical interaction with phosphoglucose isomerase, an enzyme that enables the entry of fructose into glycolysis (Yanagawa et al. 2007). The actual consequence of this interaction is unknown.

When considering carbohydrate metabolism, the regulatory mechanisms should also be mentioned. PARPs interact with HIFs, GSK3b, and AMPK, sensors that regulate glycolytic flux and the coupling of glycolysis to mitochondrial oxidation. These pathways are reviewed in Bai et al. (2015). A high-glucose or high-fructose diet can induce the expression of PARP1 (Choi et al. 2017; Huang et al. 2019). The interplay between carbohydrate metabolism and PARPs was extensively reviewed in Hopp et al. (2019).

PARPs in lipid metabolism

There is an ever-growing body of evidence for the involvement of PARPs in lipid metabolism. As a prime example, PARP2 was found to be connected to cholesterol and triglyceride metabolism in a genome-wide association study (Manunza et al. 2014).

Cellular and organismal fatty acid homeostasis are regulated by PARPs. Erener et al. (2012b) reported hypercholesterolaemia in *PARP1* knockout mice. The pattern of polyunsaturated fatty acid metabolites is dysregulated in *PARP1* knockout mice (Kiss et al. 2015) and there seems to be a correlation between PARP1 activity and erythrocyte membrane composition (Bianchi et al. 2016). Furthermore, the composition of membrane-constituent lipids was altered upon the deletion of *PARP2* (Marton et al. 2018b).

Fatty acid absorption and fatty acid biosynthesis had not been studied in the context of PARP enzymes and poly-ADP-ribosylation; however, the involvement of PARPs is likely, as suggested by scattered data in the literature. For example, the deletion of *PARP2* reduces the expression of fatty acid synthase in the white adipose tissue (Bai et al. 2007). The expression of the fatty acid transporters, FABP7, FABP3, CD36, and aP2 (FABP4), are regulated by PARP1, PARP2, and tankyrases (Bai et al. 2007; Yeh et al. 2009; Erener et al. 2012a; Kiss et al. 2015). The deletion of *PARP1*, *PARP2*, or *PARP10* induces mitochondrial fatty acid oxidation (Bai et al. 2011a,b; Márton et al. 2018a). Upon the genetic deletion of *PARP2*, the respiratory quotient decreases, suggesting a preference for fatty acid oxidation both in the active and in the sleeping period of the daily cycle (Bai et al. 2011a). Acylation of histone proteins by fatty acids may serve as epigenetic marks, a recent study suggested the PARP-sirtuin interplay may be a key factor in regulating acyl epigenetic marks (Faraone-Mennella et al. 2019).

Certain fatty acid-type lipid species can regulate the expression of PARPs. Serum deprivation of a plethora of lipid species (Sun et al. 2019) can inhibit PARP2 expression, similar to lipoic acid (Zhang et al. 2014). Caloric restriction reduces, while a high-fat diet induces the expression of PARP1 (Bai et al. 2011b; Salomone et al. 2017; Huang et al. 2019). In a similar fashion, fatty acid synthase activation or overexpression can also induce PARP1 expression (Wu et al. 2016).

Another arch of lipid metabolism is cholesterol homeostasis and the metabolism of cholesterol derivatives. The central organ for cholesterol biosynthesis is the liver, although other organs, such as skeletal muscle, also possess functional enzymatic machinery for cholesterol biosynthesis. Dietary cholesterol is taken up from the intestines and is then transported to the liver by chylomicrons. Excess cholesterol is excreted in the bile that is subsequently emptied into the intestines. Collectively, this is called the enterohepatic circulation of cholesterol. The liver can excrete cholesterol into low-density lipoprotein (LDL) that are then sent to the periphery to supply cholesterol to cells. Peripheral cholesterol is returned to the liver by high-density lipoproteins (HDL). This is the peripheral circulation of cholesterol in humans. Mice have little HDL, therefore, LDL performs the functions of HDL in mice. Cholesterol is a starting compound for the synthesis of steroid hormones, vitamin D, and bile acids.

PARP2 negatively regulates de novo cholesterol biosynthesis through suppression of sterol-regulatory element-binding protein expression. The deletion of PARP2 induces increased cholesterol biosynthesis in the liver and skeletal muscle (Szántó et al. 2014; Marton et al. 2018b). A fraction of excess cholesterol seems to be incorporated into biomembranes (Marton et al. 2018b). The deletion of *PARP2* does not affect the enterohepatic circulation of cholesterol. However, *PARP2* deletion reduces the expression of hepatic ATP-binding cassette subfamily A member 1 (ABCA1), a major transporter of cholesterol to lipoproteins (Szántó et al. 2014). In line with this, serum HDL levels are lower in *PARP2* knockout mice (Szántó et al. 2014). However, it is not easy to translate this finding into the human situation.

PARP1 expression and activity correlate negatively with ABCA1 expression (Shrestha et al. 2016). In addition, PARP1 regulates the expression of microsomal epoxide hydrolase (mEH), a key sodium-dependent bile acid transporter in hepatocytes (Peng et al. 2015). Furthermore, a lipid-activated enzyme, acyl-CoA-binding domain containing 3, activates PARP1 activity (Chen et al. 2015). Knockout and pharmacological inhibitor studies show that PARP1 inhibition improves HDL/LDL levels in mice (Diestel et al. 2003; Kiss et al. 2006; Oumouna-Benachour et al. 2007; Hans et al. 2008; von Lukowicz et al. 2008; Zerfaoui et al. 2008; Hans et al. 2009a, b; Xu et al. 2014). In humans, an SNP that renders PARP1 less active correlates with decreases total cholesterol levels, increases in HDL and decreased risk for coronary artery disease (Wang et al. 2017).

Lipids can be stored physiologically or pathophysiologically in multiple organs, where excess lipids cause damage to the tissue. Lipid-mediated activation of PARP1 may have a crucial role in organ or cellular damage (Diestel et al. 2003; Kiss et al. 2006; Hans et al. 2008; Bai and Csóka 2015; Chen et al. 2015). Ectopic lipid deposition to the walls of arteries happens in atherosclerosis. PARP inhibition or genetic deletion of *PARP1* alleviates the symptoms of atherosclerosis by reducing plaque area, lipid deposition, inflammation, and the HDL/LDL ratio (Martinet et al. 2002; Kiss et al. 2006; Ambrose et al. 2009; Liu et al. 2011; Sunderland et al. 2011; Shen et al. 2012; Wei et al. 2013; Xu et al. 2014).

The liver, although it has limited lipid storage, is also a site for abnormal lipid deposition in alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD, respectively). Alcohol consumption induces PARylation (Nomura et al. 2001). Logically, pharmacological PARP inhibition confers protection against steatosis, inflammation, and liver tissue injury in AFLD (Mukhopadhyay et al. 2017). While the genetic deletion of *PARP2* is protective against nonalcoholic hepatic lipid accumulation (Bai et al. 2011a), there is apparent ambiguity in the literature on the role of PARP1 concerning whether the genetic ablation of *PARP1* exacerbates NAFLD (Erener et al. 2012b) or pharmacological PARP inhibition protects against steatosis, inflammation, and liver tissue injury in NAFLD (Bai et al. 2011b; Gariani et al. 2017; Mukhopadhyay et al. 2017; Huang et al. 2018). The differences have not been elucidated yet.

General outline of adipogenesis

"Professional" lipid storage cells in mammals are adipocytes classified as white, brown, and beige adipocytes.

Brown or multilocular (referring to the numerous intracellular lipid droplets) adipocytes are localized to specific regions, including the interscapular and perirenal regions and lining the large arteries (Cannon and Nedergaard 2004). Brown adipocytes are characterized by high mitochondrial content and high uncoupling protein-1 (UCP1) expression (Kajimura 2015). This tissue is vital in human

newborns and in rodents for maintaining core body temperature through uncoupled respiration and through that, in maintaining organismal energy balance, regulating fatty acid and glucose oxidation, and preventing or alleviating obesity and its consequences (Cannon and Nedergaard 2004).

Beige adipocytes are localized within white adipose tissue depots mixed with white adipocytes (Wu et al. 2012). Beige cells share the morphological characteristics of white adipocytes; nevertheless, beige cells respond to adrenergic stimuli by mitochondrial biogenesis, induction of UCP1 expression, fatty acid breakdown, and heat generation. Beige adipocytes are characterized by a futile creatine cycle (Kristóf et al. 2016; Bertholet et al. 2017; Kazak et al. 2017) that is not present in brown cells and is vital for heat generation. Importantly, a mutation in the *fto* gene was associated with impaired beige adipogenesis and, consequently, impaired mitochondrial biogenesis and organismal energy balance (Claussnitzer et al. 2015).

White adipocytes are cells specialized for fat storage. Morphologically, these cells are unilocular and when stimulated respond with triglyceride breakdown through hormone-sensitive lipase (HSL). There are multiple adipose tissue depots in the body and their metabolic behavior is quite different in terms of lipid mobilizing capacity or heat generation (Garaulet et al. 2006; Roca-Rivada et al. 2011; Sacks et al. 2013; Luche et al. 2015). The switching on of beige adipocytes in white adipose depots or the transdifferentiation of white adipocytes to brown or beige cells is termed "browning" (Kajimura 2015).

According to the classical scheme of adipocyte differentiation, *Pax7*$^+$ *Myf5*$^+$ brown cell precursors segregate from the dermatomyotome, while *Pax7*$^-$ *Myf5*$^-$ stem cells differentiate to white and beige adipocytes (Rosen and Spiegelman 2014). This picture is, in fact, more complex (Fig. 1). Lineage tracing studies revealed that there are multiple lineages giving rise to white adipocytes. The majority of these are of mesenchymal origin; nevertheless, depots in the head region stem from the neural crest (*Sox10*$^+$, *Wnt1*$^+$ precursors) (Billon et al. 2007; Sanchez-Gurmaches and Guertin 2014a). Mesenchymal precursors can be *Myf5*$^+$ or *Myf5*$^-$. The proportion of white adipocytes derived from *Myf5*$^+$ or *Myf5*$^-$ precursors vary between the adipose tissue depots (Sanchez-Gurmaches and Guertin 2014a). Beige adipocytes can differentiate from the same precursors as the white adipocytes, except for neural crest-derived precursors (Sanchez-Gurmaches and Guertin 2014a). Finally, brown adipocytes differentiate from *Pax7*$^+$ *Myf5*$^+$ dermatomyotomal precursors (Sanchez-Gurmaches and Guertin 2014a).

The in vitro models of (human) adipose tissue-derived stem cells (hADMSCs), (embryonic) fibroblasts, or immortalized cell lines (e.g., 3T3-L1, 3T3-F442A, etc.) (Ruiz-Ojeda et al. 2016) are useful tools in understanding transcriptional control over adipogenesis. The differentiation protocol usually involves a complete stop of proliferation by growing cells at confluency, followed by the induction of differentiation by a cocktail of hormones including insulin, a synthetic glucocorticoid, dexamethasone, and 3-isobutyl-1-methylxanthine (IBMX), a phosphodiesterase inhibitor. After the induction of differentiation, cells undergo commitment and committed cells undergo a few rounds of cellular division, called mitotic clonal expansion (Fig. 2). It is not known whether clonal expansion also characterizes the in vivo differentiation of adipocytes. After clonal expansion, cells begin accumulating lipids in lipid droplets (in vitro differentiated adipocytes are multilocular), termed terminal differentiation (Fig. 2; Ruiz-Ojeda et al. 2016; Mota de Sa et al. 2017).

Concerted action of a large set of transcription factors is needed to guide adipogenic differentiation ((Fig. 2; Mota

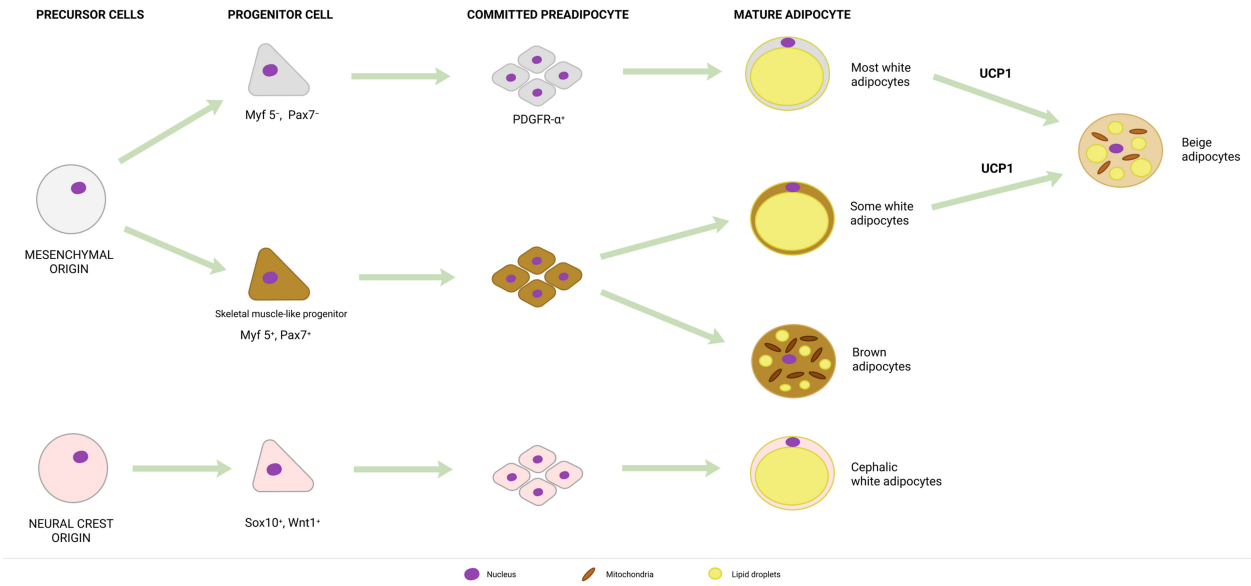

Figure 1. The general scheme of adipose tissue lineage differentiation. Abbreviations are defined in the text.

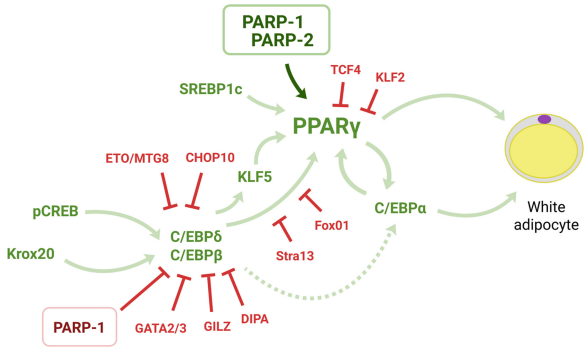

Figure 2. The involvement of PARP enzymes in the transcriptional control of white adipogenesis. Abbreviations are defined in the text.

de Sa et al. 2017). Adipogenic transcription factors interacting with PARPs are listed in Table 3. Classically, clonal expansion of white adipocytes was shown to be mediated by the self-amplifying activation of C/EBPδ and C/EBPβ that subsequently induces the expression of C/EBPα and, finally, the expression of peroxisome proliferator activated receptor (PPAR) γ1 and PPARγ2 expression (Fajas et al. 1998).

PPARγ1 and PPARγ2 belong to the family of nuclear receptors and are crucial in driving adipogenesis and adipocyte function through supporting the expression of major adipogenic genes (Fajas et al. 1998). PPARγ-dependent genes include lipoprotein lipase (LPL), fatty acid transporters (CD36 and aP2), TG storage proteins (e.g., perilipin), and adipokines (e.g., leptin, adiponectin) (Auwerx et al. 2003). While PPARγ1 is expressed ubiquitously, PPARγ2 expression is restricted to adipocytes and macrophages (Fajas et al. 1997; Nagy et al. 1998). Both PPARγ isoforms are lipid activated, suggesting an intricate modulation of PPARγ activity by lipid species (Nagy et al. 1998). The ligand-mediated activation of PPARγ involves the exchange of repressor cofactors (e.g., NCoR-1) to coactivator factors (e.g., p300) that facilitate chromatin relaxation and the initiation of transcription (Gelman et al. 1999; Coste et al. 2008).

The induction of the expression of PPARγ isoforms is a common denominator of beige and brown adipogenesis, similar to white adipogenesis. Mitochondrial biogenesis is a key factor for the differentiation of beige and brown adipocytes. The concerted action of the energy stress sensor web is vital for the induction of mitochondrial biogenesis, including the activation of AMPK or SIRT1 (Qiang et al. 2012; Shan et al. 2013; Wang et al. 2015; Abdul-Rahman et al. 2016; Nagy et al. 2019).

Table 3. *Interactions between proadipogenic transcription factors and the PARylation machinery*

Transcription factor	Role in adipogenesis	Interacting PARP	Role of PARP	References
C/EBPβ	Promote clonal expansion	PARP1	PARP1 interacts with C/EBPβ and PARylates C/EBPβ	Luo et al. 2017
AP-1	Promote clonal expansion	PARP1	Positive regulator of AP-1	Oliver et al. 1999
PPARγ/RXR complex	Promote terminal differentiation	PARP1	PARP1 is a positive cofactor of the PPARγ/RXR complex	Huang et al. 2009; Erener et al. 2012a; Lehmann et al. 2015
		PARP2	PARP2 is a positive cofactor of the PPARγ/RXR complex	Bai et al. 2007
SREBP1	Promote terminal differentiation	PARP2	PARP2 is a negative regulator of SREBP1 expression	Szántó et al. 2014; Marton et al. 2018b
GR	Promote terminal differentiation	PARP1	GR and PARP1 are interacting partners	Muthumani et al. 2006
SMAD 1, 5, 8	Promote terminal differentiation	PARG	PARG can de-PARylate and activate SMAD3	Marques et al. 2019
GATA transcription factors	Inhibit clonal expansion	PARPi	PARP inhibition inhibits GATA3 expression and promoter binding	Datta et al. 2011
SMAD 2, 3	Inhibit terminal differentiation	PARP1/-2	PARP1 and PARP2 are negative factors in SMAD3 signaling.	Lónn et al. 2010; Dahl et al. 2014
ER	Inhibit terminal differentiation		PARP1 and PARP2 are positive regulators of ERα.	Ju et al. 2006; Bai et al. 2007; Szántó et al. 2012; Zhang et al. 2013
AR	Inhibit terminal differentiation	PARP1	PARP1 is a positive regulator of AR.	Shi et al. 2008; Schiewer et al. 2012; Gui et al. 2019
β-Catenin	Inhibit clonal expansion and terminal differentiation	TNK, PARP1	PARP1 is a positive regulator of β-catenin accumulation	Nozaki et al. 2003; Idogawa et al. 2005; Mariotti et al. 2017

Most of these interactions were shown in model systems other than adipogenesis.
(C/EBP) CCAAT enhancer-binding protein; (AP-1) activator protein 1; (RXR) retinoid X receptor; (PPAR) peroxisome proliferator activated receptor; (SREBP) Sterol regulatory element-binding protein; (GR) glucocorticoid receptor.

The role of PARP enzymes in adipogenesis

The first observation that PARPs modulate adipogenesis came in 1995 by Smulson et al. (1995) using the 3T3-L1 model system and 3AB, a rather unspecific PARP inhibitor. This study showed that pharmacological PARP inhibition hampers 3T3-L1 differentiation (Smulson et al. 1995). Indeed, PARPs play a role in the regulation of adipogenesis and adipose tissue function. Since this first observation, much data has emerged along with numerous controversial issues.

Early commitment and clonal expansion

PARP1, PARP2, and PARP7 have pivotal roles in decision making between retaining stem cell properties and differentiation in nonadipogenic models (Yélamos et al. 2006; Farrés et al. 2013, 2015; Nozaki et al. 2013; Roper et al. 2014; Vida et al. 2016). Therefore, PARPs may be crucial in the early commitment of cells toward preadipocytes and adipose lineages (Fig. 1). To date, no studies have been published concerning the role of PARPs in commitment to adipocyte lineages in an in vivo setting (e.g., as in Sanchez-Gurmaches and Guertin 2014b). However, PARP1 has a crucial role in preadipocyte commitment to white adipocyte differentiation in in vitro systems (Luo et al. 2017; Ryu et al. 2018).

In the in vitro differentiation of 3T3-L1 preadipocytes, a characteristic PARylation pattern was detected (Luo et al. 2017). In confluency (growth arrest), PARP1 auto-PARylation dominates cells, after which the PARylation signal is low in the clonal expansion phase and boosts again in terminal differentiation (Luo et al. 2017). In terminal differentiation, PARP1 auto-PARylation returns, nevertheless, lower molecular weight PARylation signals are also detected (Luo et al. 2017).

As noted in the previous chapter, the clonal expansion phase is dominated by the self-intensifying loop between C/EBPβ and C/EBPδ. This loop is vital for the subsequent transcription of C/EBPα and PPARγ transcription factors that then transcribe the "executors" of lipogenesis. 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*. Hence, genetic or pharmacological inactivation of PARP1 supports adipocyte differentiation (Luo et al. 2017). The deletion of these PARylation sites enhance C/EBPβ binding to target promoters and renders C/EBPβ resistant to PARP inhibitors. These findings provide a physiological explanation for reduced PARylation during the clonal expansion phase.

Another mechanism for the regulation of PARP1 activity and clonal expansion is the compartment-specific NAD^+ biosynthesis through NMNAT enzymes. Ryu et al. (2018) showed that blocking nuclear NMNAT-1 induces adipocyte differentiation through limiting nuclear NAD^+ for PARP1. In other words, PARP1 activation and fueling PARP1 activation by NMNAT-1 can keep preadipocytes undifferentiated. The cytosolic NMNAT-2 is induced early in adipocyte differentiation (4 h after induction) and shifts nuclear NAD^+ biosynthesis to the cytosol to support glycolysis (Ryu et al. 2018). As a "side effect," nuclear PARylation is reduced, supporting white adipocyte differentiation (Ryu et al. 2018).

Adipocyte terminal differentiation

Adipocyte terminal differentiation in in vitro models is characterized by increasing C/EBPα and PPARγ protein expression and lipid accumulation. This phase of terminal differentiation is associated with the accumulation of PARP1 and PAR formation (Erener et al. 2012a; Luo et al. 2017). In the studies of Erener et al. (2012a,b), pharmacological and genetic PARP inhibition blocked the differentiation of 3T3-L1 cells. When PARP1 was blocked in the course of 3T3-L1 differentiation, a major reduction in the expression of C/EBPα and PPARγ2 and a set of PPARγ-dependent transcripts was observed, in stark contrast to the previously discussed studies (Luo et al. 2017; Ryu et al. 2018).

Lower adipocyte differentiation was linked to a slower resolution of transcription-coupled topoisomerase II-inflicted double strand breaks and the consequent slower initiation of RNA polymerase II-mediated transcription in the absence of PARP activity (Pavri et al. 2005; Erener et al. 2012a; Lehmann et al. 2015). Furthermore, PARP inhibition supported the binding of NCoR-1 (an inhibitory cofactor of PPARγ), while decreasing the binding of p300 (an activating cofactor of PPARγ) (Lehmann et al. 2015). In a cardiomyocyte model, pharmacological, and genetic PARP1 inhibition led to increased PPARγ activity (Huang et al. 2009), in contrast to the observations detailed above.

There is apparent contradiction between the results showing that PARP1 and NAD^+ biosynthesis during the commitment phase blocks (Luo et al. 2017; Ryu et al. 2018), while during terminal differentiation PARP1 supports adipocyte differentiation (Erener et al. 2012a,b; Lehmann et al. 2015). To date, no explanation is given to the discrepancies that is backed by experimental proof. Nevertheless, the visibly contradictory results may be both true. The contradictory reports do observe PARP auto-PARylation in confluent and in terminally differentiated cells (Erener et al. 2012a; Luo et al. 2017) suggesting that similar processes may take place in all cases; however, the dependence of the cells on early commitment may be different. In our hands different clones of the 3T3-L1 cells have different behavior in differentiation and response to PARP inhibitors (unpublished data).

The genetic silencing of PARP2 led to lipodystophy in chow diet-fed mice, which was mirrored when primary fibroblasts were differentiated to mature adipocytes (Bai et al. 2007). Decreased adipocytic differentiation was a result of blunted PPARγ activation. PARP2 binds to PPARγ-mediated promoters (e.g., *aP2*) and supports mRNA transcription. Reduced expression of the PPARγ-dependent genes in the PARP2 knockout mice points toward hampered PPARγ activation in the absence of PARP2 (Bai et al. 2007).

In the above-mentioned studies (Bai et al. 2007; Huang et al. 2009; Erener et al. 2012a,eb; Lehmann et al. 2015; Luo et al. 2017; Ryu et al. 2018), PARP inhibition or the

genetic deletion of *PARP1* or *PARP2* modulated genes involved in fatty acid uptake (lipoprotein lipase [*LPL*], fatty acid binding protein 4 [*FABP4*, *aP2*], and *CD36*), lipid storage (*perilipin*), fatty acid biosynthesis (fatty acid synthase [*FAS*]), and adipokines (*leptin*, *adiponectin*, and *resistin*) in white adipocyte differentiation models. The deletion of *tankyrase-1* induced leptin and adiponectin expression and secretion from white adipose tissue (Yeh et al. 2009). These genes are PPARγ-dependent and encompass all processes needed for triglyceride uptake and storage. To date, no studies have reported fatty acid release disorders in relation to the modulation of PARP1 or PARP2 activity (Bai et al. 2007; Erener et al. 2012b).

Switch between white, brown, or beige adipogenesis

PARPs may have a role in selecting between the differentiation to white, brown, and beige adipocytes. PARP1 and PARP2 were shown to modulate skeletal muscle myoblast differentiation and health (Butler and Ordahl 1999; Vyas et al. 2001; Hu et al. 2013; Chacon-Cabrera et al. 2015). Therefore, it is also likely that PARPs can influence white/brown/beige diversion. This hypothesis is further supported by the widespread interactions between energy stress sensors, mitochondrial biogenesis regulators, and PARPs (Bai et al. 2015).

The deletion of *PARP1* or *PARP2*, as well as the pharmacological inhibition of PARP, supports mitochondrial biogenesis (Virag et al. 1998a; Bai et al. 2011a,b,2015; Szanto et al. 2011; Mohamed et al. 2014) via the preservation of cellular NAD^+ pools and the subsequent activation of the SIRT1–PGC1α axis (Cantó et al. 2013; Bai et al. 2015). In agreement with this, Nagy et al. (2019) found that in vitro treatment of hADMSC cells, differentiated to white adipocytes, with olaparib induced browning of the cells, marked by mitochondrial biogenesis and UCP1 induction. In the olaparib-treated cells, beige cell markers were not induced, suggesting browning induced transdifferentiation to brown adipocytes. In good agreement with that observation, in *PARP1* knockout mice, we detected more active brown adipose tissue (lower lipid deposition, induction of UCPs, increased fatty acid oxidation, and higher mitochondrial content), increased energy expenditure, and improved capacity to withstand cold exposure (Bai et al. 2011b). We detected increased cellular NAD^+ content and SIRT1 activity in both models (Bai et al. 2011b; Nagy et al. 2019). Interestingly, the brown adipose tissue of the *PARP2* knockout mice was not more active (Bai et al. 2011a). To date, no thorough studies were performed to assess the contribution of PARPs to beige and brown adipocyte differentiation. These findings are in agreement with the observations that better NAD^+ availability (Yamaguchi et al. 2019) or SIRT1 activation supports brown and beige differentiation (Qiang et al. 2012; Khanh et al. 2018).

Lipid accumulation, obesity, insulin sensitivity

A role for PARP enzymes in obesity has been reported. In a study of monozygotic twins, higher PARP activity was found in the subcutaneous white adipose tissue of the heavier cotwin (Jukarainen et al. 2016). Furthermore, in weight loss adipocytic PARP activity is reduced, while SIRT1 activity is up-regulated (Rappou et al. 2016). In murine studies, PARP1, PARP2, and tankyrase-1 were shown to be involved in modulating energy balance and obesity. Similar to the ambiguity in the role of PARP1 in adipocyte differentiation, the studies on the organismal role of PARP1 in obesity and its consequences are also contradictory. In our studies, *PARP1* knockout mice were leaner when kept on chow diet that was accentuated on high-fat feeding (Bai et al. 2011b). This study was backed by a study from another laboratory. PARP1 knockout mice had lower body weight and white adipose tissue mass when on a high-fat diet (Erener et al. 2012b). Furthermore, treatment of mice with an orally administered PARP inhibitor, MRLB-45696, (PARP1 is responsible for 80%–85% of total cellular PARP activity) (Schreiber et al. 2002; Szanto et al. 2011) prevented weight gain on a high-fat diet (Lehmann et al. 2015). In contrast to these studies, a report by Devalaraja-Narashimha and Padanilam (2010) reported a complete opposite phenotype; the *PARP1* knockout mice became seriously obese as compared with their wild-type counter partners upon high-fat feeding. In all studies, a hypercaloric high-fat diet was used.

Obesity is a complex pathology and cannot be solely attributed to the dysfunction of white adipocytes; a complex deregulation of organismal energy homeostasis is involved (Rosen and Spiegelman 2014). In the above-mentioned studies that reported a lean phenotype, an energy expenditure phenotype was described due to mitochondrial biogenesis in the brown adipose tissue and the skeletal muscle, attributed mainly to the activation of the NAD^+–SIRT1 axis (Bai et al. 2011b; Pirinen et al. 2014; Lehmann et al. 2015). The improved metabolic fitness yielded improved glucose tolerance and insulin sensitivity, with skeletal muscle being responsible for glucose clearance both in chow-fed and high-fat-fed mice (Bai et al. 2011b). In the monozygotic twin study, the activation of the NAD^+–SIRT1 axis and the consequently lower PARP activity was associated with a leaner, metabolically healthier phenotype (Jukarainen et al. 2016). The contradictory study (Devalaraja-Narashimha and Padanilam 2010) reported an opposing rearrangement of energy homeostasis characterized by lower oxygen consumption, energy deliberation, worsened glucose clearance, and insulin resistance.

These are again opposing results without good experimental explanation. A root cause for the disagreement between the studies could be that these studies were conducted on two different knockout *PARP1* mouse strains. One of the strains was generated by Wang et al. (1995) and deposited at Jackson Laboratories; the other strain was generated in the laboratory of de Murcia et al. (1997). The mice generated by Wang et al. (1995) were on an SV129 background, while the mice generated by de Murcia et al. (1997) were on a C57/Bl6J background. The metabolic behavior of the two different backgrounds is profoundly different (Andrikopoulos et al. 2005; Berglund et al. 2008) and might be the explanation for the

differing results. A solution for these issues could be the use of a transgenic *PARP1loxP* mouse strain that will bypass developmental issues and enable the study of interorgan interactions (JAX 2019).

Induction of mitochondrial biogenesis by enhancing the NAD^+–SIRT1 axis in the skeletal muscle after the genetic deletion of *PARP2* brought about a lean phenotype (Bai et al. 2011a; Mohamed et al. 2014). Interestingly, the brown adipose tissue of the *PARP2* knockout mice was not involved in the energy expenditure phenotype, in contrast to the *PARP1* knockout mice (Bai et al. 2011a,b). In chow-fed mice, the deletion of *PARP2* improved insulin sensitivity and glucose clearance. While on a high-fat diet, the ablation of *PARP2* improved insulin sensitivity, but insulin secretion and glucose clearance were blunted due to inhibition of compensatory β-cell proliferation (Bai et al. 2011a).

Tankyrase expression is among the highest in the white adipose tissue and the brain (Yeh et al. 2009). White adipose tissue and energy homeostasis changes were observed in *tankyrase* knockout mice (Yeh et al. 2007, 2009). Interestingly, tankyrase expression may also affect brown adipose tissue (Yeh et al. 2009). However, the involvement of tankyrase in brown adipose tissue function was not investigated yet. Tankyrase knockdown was shown to impair Glut4 translocation and hence insulin-stimulated glucose uptake, resulting in down-regulation of glucose metabolism in differentiated 3T3-L1 adipocytes (Yeh et al. 2007). These effects were dependent on tankyrase activity (Yeh et al. 2007). In *tankyrase* knockout mice, the relative mass of the epididymal white adipose tissue decreased in parallel to enhanced energy expenditure marked by increased oxygen consumption (Yeh et al. 2009).

Future directions

PARP enzymes and PARP inhibition interfere with adipose tissue biology at multiple points. There are obesity-associated processes (e.g., inflammation) that are also PARP regulated, but their interplay had not been assessed. We give a brief overview of these processes below.

Inflammation plays diverse roles in obesity and adipose tissue homeostasis. Obesity is associated with inflammation and fibrosis of the adipose tissue (Reilly and Saltiel 2017). Preventing adipose tissue inflammation is a key step toward the "metabolically healthy" obese phenotype (Vishvanath and Gupta 2019). Furthermore, inflammatory signaling seems to be a player in diverting toward the beige lineage (Sun et al. 2018). PARP enzymes are involved in the regulation of inflammation; usually, the absence of PARP1 or PARP2 or pharmacological PARP inhibition is anti-inflammatory (Fehr et al. 2020), except for Th17-mediated processes (Kiss et al. 2019). Furthermore, increases in SIRT1 activity, which can be elicited by PARP inhibition, can suppress adipose tissue inflammation, and hence support its function (Gillum et al. 2011; Chalkiadaki and Guarente 2012). Importantly, there is evidence that the results of murine PARP inhibitor studies are likely translatable to humans (Morrow et al. 2009). PARP1 and PARP inhibition regulate IL6 (Lehmann et al. 2015), IL12m, IL13ra, SAA3, pu1, and MPEG1 (Erener et al. 2012b) expression. In the adipose tissue of *PARP2* knockout mice, signs of inflammation were detected, including F4/80 positive cells and dilated capillaries, that were absent in their wild-type counter partners (Bai et al. 2007). Whether inflammatory processes are the cause or consequence of the distortion of adipose tissue function is unknown.

Recent studies showed that the loss of microbiome diversity hampers adipose tissue browning (Suárez-Zamorano et al. 2015; Li et al. 2019). Intriguingly, the genetic deletion of PARP1 enhances the diversity of the gut microbiome (Larmonier et al. 2016; Vida et al. 2018), suggesting a possible link between PARP1 and adipose tissue browning. Disruption of circadian entrainment of feeding can also contribute to obesity (Hatori et al. 2012; Zarrinpar et al. 2016; Chaix et al. 2019) and, as noted earlier, the disruption of PARP1 leads to changes in the diurnal cycle of feeding and metabolism (Asher et al. 2010; Bai et al. 2011b). PARP activation can be a go/no-go signal in cell death (Virág et al. 1998b; Fatokun et al. 2014; Dawson and Dawson 2017) and PARPs regulate cellular proliferation (Bai 2015), two vital steps to adipocyte differentiation and selection between beige, brown, or white lineages. Similarly, PARP1 and PARP10 were implicated in the regulation of autophagy and mitophagy (Muñoz-Gámez et al. 2009; Kleine et al. 2012), processes that shape adipocyte differentiation (Kim and Lee 2014). PARPs affect nuclear structure and the epigenetic code (Wacker et al. 2007; Krishnakumar et al. 2008; Hottiger 2015; Zhao et al. 2015). PARP1 deficiency was shown to modulate H3K9me3 and H3K4me3 methylation during adipogenic differentiation (Erener et al. 2012a). Nevertheless, large scale studies are missing. There are genes reported to be PARP-mediated (e.g., *MDH1*) (Hopp et al. 2019) that regulate adipocyte differentiation. Again, the involvement of these genes in adipogenesis in the context of PARylation had not been assessed.

All adipose tissue depots are characterized by secretion of bioactive compounds such as peptide hormones (adipokines), bioactive lipids (lipokines), and RNA molecules with local (paracrine) and systemic (endocrine) effects on multiple metabolic tissues and the cardiovascular system. These bioactive compounds are synthesized and secreted as a function of the energy status of adipose tissues, which in turn regulates appetite, thermogenesis, glucose, and lipid metabolism (Scheja and Heeren 2019). The role of PARPs had not been studied in this direction. Along the same lines, large-scale endocrine studies are also missing.

The role of PARPs in adipogenesis and metabolism will clearly have practical applications not only in the strict sense of metabolism and metabolic diseases, but also from the perspective of cancer and cancer cachexia (Chacon-Cabrera et al. 2015, 2017; Barreiro and Gea 2018; Doles et al. 2018). These outstanding issues warrant further studies in the future.

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