TITLE

PARP, transcription and chromatin modeling

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Abbreviations

ABCA1, ATP-binding cassette transporter A1
ADP-ribosylation, adenosine diphosphate ribosylation
ALC1, Amplified-in-liver-cancer 1
AR, Androgen receptor
ARH3, ADP-ribosylhydrolase 3
ART, ADP-ribosyl transferase
ASF/SF2, Alternative splicing factor/splicing factor 2
BAL, B-aggressive lymphoma
Brg1, BRM/SWI2-related gene 1
CENPA, Centromere protein A
CENPB, Centromere protein B
CHD1L, Chromodomain helicase DNA binding protein 1-like
CHD4, Chromodomain helicase DNA-binding protein 4
CP190, Centrosomal protein 190
CRM1, Chromosome region maintenance 1
CTCF, CCCTC-binding factor
DDR, DNA-damage response
dMi-2, Drosophila Mi-2
DSB, Double-strand break
ENPP/NPP, ectonucleotide pyrophosphatase/phosphodiesterases
ER, Estrogen receptor
FACT, Facilitates chromatin transcription
GSK3b, Glycogen synthase kinase 3 beta
H1, Histone 1
HP1, Histone protein 1
HPF1, Histone PARylation factor 1
Hsp70, Heat-shock protein 70
hSSB1, human ssDNA-binding protein 1
iPSC, induced pluripotent stem cells
ISWI, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5

LPR16, Macro domain containing 1
 LXR, Liver X receptor
 MDM2, Mouse double minute 2
 NAD⁺, Nicotinamide adenine dinucleotide
 NELF, Negative elongation factor
 NF- κ B, Nuclear factor kappa-light-chain enhancer of activated B cells
 NR, Nuclear receptor
 NUDIX, Nucleoside diphosphate linked to another moiety X
 NuMA, Nuclear mitotic apparatus
 NURD, Nucleosome Remodelling and Deacetylation
 OAADPR, *O*-acetyl-ADP-ribose
 OB fold, oligonucleotide/oligosaccharide binding fold
 OSKM, Oct4, Sox2, Klf-4 and c-Myc
 PAR, poly(ADP)ribose
 PARG, poly(ADP)ribose glycohydrolase
 PARP, poly(ADP)ribose polymerase
 PBM, PAR-binding motif
 PBZ, PAR-binding zinc finger
 PELP1, Proline, glutamate and leucine rich protein 1
 PcG, Polycomb group bodies
 Plk1, Polo like kinase 1
 PolII, Polymerase II
 PPAR γ , Peroxisome proliferator-activated receptor- γ
 PPRE, PPAR γ response elements
 PTM, Posttranslational modification
 rDNA, ribosomal DNA
 RNF8/RNF168, Ring finger protein 8/Ring finger protein 168
 RXR, Retinoid X receptors
 SET7/9, SET domain containing lysine methyltransferase 7/9
 SIRT1, Sirtuin 1
 SMARCA5/SNF2H, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5/
 Smarca4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4
 Spt16, Suppressor of Ty 16 homolog
 SSB, Single-strand break
 SSRP1, Structure specific recognition protein 1
 TARG1, Terminal ADP-ribose glycohydrolase 1
 TIF1, Transcription intermediary factor
 TRF1, Telomeric repeat-binding factor 1
 TRF2, Telomeric repeat-binding factor 2
 WWE domain, named after aminoacids Tryptophan-Tryptophan-Glutamate
 XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1

Abstract

Compaction mode of chromatin and chromatin highly organised structures regulate gene expression. Posttranslational modifications, histone variants and chromatin remodelers modulate the compaction, structure and therefore function of specific regions of chromatin. The generation of poly(ADP-ribose) (PAR) is emerging as one of the key signalling events on sites undergoing chromatin structure modulation. PAR is generated locally in response to stresses. These include genotoxic stress but also differentiation signals, metabolic and hormonal cues. A picture emerges in which transient PAR formation is essential to orchestrate chromatin remodelling and transcription factors allowing the cell to adapt to alteration in its environment. This review summarizes the diverse factors of ADP-ribosylation in the adaptive regulation of chromatin structure and transcription.

Graphical abstract

TEXT

1.1. ADP-ribosylation – revival of the old PTM

Even though the number of posttranslational modifications (PTMs) is constantly growing thus opening new avenues of research, recent reports prove that even some of the most established and widely conserved PTMs pose significant challenges in understanding their complex function (Verdin and Ott, 2015). One of these elusive PTMs is ADP-ribosylation. ADP-ribosylation is the process during which a molecule of adenosine diphosphate ribose (ADP-ribose) is transferred from NAD⁺ molecule onto specific residues of the target protein (Chambon et al., 1963). The amino acids accepting the modifications are most commonly glutamate, aspartate and arginine, but some other amino acids have been also reported as acceptors ((Barkauskaite et al., 2015; Rosenthal and Hottiger, 2014; Vyas et al., 2014). A major family of enzymes that generates ADP-ribosylation are poly-ADP-ribose-polymerases (PARPs) (Schreiber et al., 2006). PARPs can transfer one ADP-ribose molecule generating mono(ADP-ribosyl)ation or chains of poly(ADP-ribose) (PARylation) onto a specific acceptor site in the protein target. PARP1 for example can make chains of more than 100 nucleotide units. Additionally, PARP1 can form branched chains every 20-50 ADP-ribose units (D'Amours et al., 1999). Since PAR chain forms a helicoidal secondary structure that is similar to RNA and DNA, PAR can be considered as the third nucleic acid (D'Amours et al., 1999). Phylogenetic studies reveal that ADP-ribosylation is an ancient and conserved PTM: it is found in almost all organisms from bacteria to eukaryotes with the exception of yeast (Perina et al., 2014). The involvement of protein ADP-ribosylation in main cellular processes such as DNA damage response (DDR), transcription, chromatin architecture and plasticity, differentiation and metabolism has been well investigated and documented (recently reviewed in (Bai, 2015; Barkauskaite et al., 2015; Canto et al., 2015; Dantzer and Santoro, 2013; Gibson and Kraus, 2012; Hottiger, 2015). Overall, ADP-ribosylation seems to act as a mediator of stress response upon DNA damage, modulations of metabolic requirements during differentiation, response to changed environmental signals and metabolic milieu facilitating the adaptation of the cell to new situation (Figure 1.).

1.2. Writers, readers and erasers of ADP-ribosylation

ADP-ribosylation is a highly dynamic PTM, which needs to be tightly regulated in time and space. Accordingly, all organisms possessing ADP-ribosylation have developed networks of enzymes of varying complexity involved in modulation of ADP-ribosylation signalling. As with other PTMs, ADP-ribosylation system has its “writers”, “readers” and “erasers” (Table 1.).

Writers

PARP family encompassing the “writers” in most of the mammals has at least 16 members. The most studied member is PARP1 shown to be crucial for the control of several cellular processes (Ame et al., 2004; Bock and Chang, 2016). All PARP enzymes possess a highly conserved ADP-ribosyl transferase (ART) domain. Differential activity between the PARPs can be achieved via slight variations in the ART domain (Steffen and Pascal, 2013). For example, while PARP1, PARP2 and tankyrases can make longer chains, many of other PARPs'

activity is restricted to mono-ADP-ribosylation or generation of very short chains. Structural implications for the activity of PARPs were summarized recently elsewhere and will not be discussed here (Barkauskaite et al., 2015; Steffen and Pascal, 2013; Vyas et al., 2014). The complexity of ADP-ribosylation function is particularly enhanced in higher organisms whose PARP enzymes comprise, in addition to the ART domain, a plethora of other domains that additionally regulate the PARPs activity and functional specificity (Kalisch et al., 2012).

Readers

The macrodomain fold is found in numerous proteins from viruses to eukaryotes and is able to bind or sense different ADP-ribose metabolites (for more details please refer to (Posavec et al., 2013; Rack et al., 2016)) and macrodomain containing proteins such as ALC1 and macroH2A (Ahel et al., 2009; Kustatscher et al., 2005; Timinszky et al., 2009) serve as readers of protein ADP-ribosylation signals (see chapters 3.1.1 and 4.). Apart from macrodomain several other domains have been described as readers, for example PBM (Pleschke et al., 2000), PBZ (Ahel et al., 2008), WWE (Wang et al., 2012)) and OB fold (Zhang et al., 2014) (reviewed in (Barkauskaite et al., 2013b; Gibson and Kraus, 2012; Kalisch et al., 2012; Karlberg et al., 2013)).

Erasers

Several proteins have been described to be able to degrade PAR polymer or to remove protein mono(ADP-ribosyl)ation from targets. These include PAR glycohydrolase (PARG), ARH3, MACROD1 (LPR16), MACROD2 and terminal ADP-ribose hydrolase (TARG1 or C6ORF130) (Barkauskaite et al., 2013a; Jankevicius et al., 2013; Mueller-Dieckmann et al., 2006; Rosenthal et al., 2013; Sharifi et al., 2013; Slade et al., 2011). Apart from ARH3, all of these erasers have the catalytic macrodomain fold in common, that supports both binding and hydrolysis function for these enzymes. While PARG and ARH3 degrade the PAR chains, the other three enzymes, MACROD1, MACROD2 and TARG1 remove the protein-proximal mono-ADP-ribose and enable the complete reversal of the modification (Steffen and Pascal, 2013). The by-product of sirtuin enzymatic activity, *O*-acetyl-ADP-ribose (OAADPR), can also be hydrolysed by MACROD1/D2 and TARG1 (Chen et al., 2011; Peterson et al., 2011). Other families of proteins that may remove the protein ADP-ribosylation are nucleoside diphosphate linked to another moiety X proteins (NUDIX) (Palazzo et al., 2015) and ectonucleotide pyrophosphatase/phosphodiesterases (ENPP/NPP) (Palazzo et al., 2016).

Table 1. List of writers, readers and erasers of ADP-ribosylation

WRITERS			READERS	ERASERS
PARP1	Poly	Macro domain	ALC1, macroH2A1.1,	ARH1
PARP2	Poly		MACROD1, MACROD2,	ARH3
PARP3	Mono		PARP9, PARP14, PARP15,	ENPP/NPP
PARP4	Mono			MACROD1
PARP5a	Poly/oligo	OB fold	hSSB1	MACROD2
PARP5b	Poly/oligo			NUDIX
PARP6	Mono	PBM	ATM, CENPA, condensin 1, DNA ligase III, DNA-PK catalytic subunit, DNA polymerase ϵ , ERCC-6, Ku70, MR11, MSH6, p21, p53, XPA, XRCC1,	PARG
PARP7	Mono			TARG1
PARP8	Mono			
PARP9				
PARP10	Mono	PBZ	APLF, CHFR	
PARP11	Mono			
PARP12	Mono			
PARP13				
PARP14	Mono	WWE domain	RNF146, PARP14, PARP11, PARP12, PARP13, deltex 1, deltex 2, deltex 4, HUWE1, TRIP12, DDHD2	
PARP15	Mono			
PARP16	Mono			

PARP9 and PARP13 are inactive. Poly, poly(ADP)-ribosylation. Mono, mono(ADP)-ribosylation. Oligo, oligo(ADP)-ribosylation. For readers, their functional domains are named.

2. PARPs in DNA repair and beyond

PARP1 and PARP2 are major responders to DNA damage, including both single-strand (SSB) and double-strand (DSB) DNA breaks (El-Khamisy et al., 2003). Following genotoxic insult PARP1 and PARP2 sense DNA damage by binding to the broken DNA ends and are specifically and rapidly activated to induce gross ADP-ribosylation of themselves and their target proteins (including histones). This PARylation signals essential downstream events in DNA repair and chromatin structure regulation such as recruitment of other DDR genes (Dabin et al., 2016; Tallis et al., 2014). The functional importance of PARP1 and PARP2 *in vivo* for DDR is demonstrated by the fact that both *Parp1*^{-/-} and *Parp2*^{-/-} mice show increased genomic instability and sensitivity to ionizing irradiation and other DNA-damaging agents (Luo and Kraus, 2012). However, it is likely that PARP1 and PARP2 exhibit partially overlapping functions since whilst mice can survive without *Parp1* or *Parp2*, they show embryonic lethality when devoid of both (Menissier de Murcia et al., 2003).

Recently solved PARP1-DNA structures demonstrate the molecular basis of PARP activation upon binding to DNA breaks (Ali et al., 2012; Eustermann et al., 2015; Langelier et al., 2011, 2012). PARP1 binds the deformed DNA with the N-terminally located zinc finger domains, co-operatively controlling the C-terminal enzymatic activity (Eustermann et al., 2015). The Luger lab has further demonstrated that for the optimal activation PARP1 prefers nucleosome with extensions of DNA on both ends (Clark et al., 2012). Once PARP1 is activated and synthesises PAR chains, the scaffold for the recruitment of DNA repair complexes is created (Masson et al., 1998; Schreiber et al., 2002) and proteins that contain the PAR binding modules recruit these complexes to sites of PAR generation. One

of the first proteins to be recruited to PAR is XRCC1 (Okano et al., 2003) that organises the DNA break repair ligase complexes (Caldecott, 2003). Chromatin remodelers and histone chaperones also assist in DDR, for example ALC1 and APLF bind PAR through their macro and PBZ modules respectively (Ahel et al., 2009; Gottschalk et al., 2009; Mehrotra, 2012). Another DDR mediator is the p53 protein, a transcription factor that can interact with PAR and subsequently becomes PARylated by PARP1 (Malanga et al., 1998; Mendoza-Alvarez and Alvarez-Gonzalez, 2001; Valenzuela et al., 2002; Wesierska-Gadek et al., 1996).

Another PARP directly involved in DNA break repair is PARP3. PARP3 was first characterized a decade ago when it was demonstrated to co-localise to the regions of pericentric heterochromatin in the nucleus with Polycomb group bodies (PcG) and factors involved in DSB repair (Loseva et al., 2010; Rouleau et al., 2007; Rulten et al., 2011). Later, PARP3 was specifically shown to interact with PARP5a/tankyrase 1 and mitotic factor NuMA. PARP3 stimulated ADP-ribosylation of NuMA both directly and indirectly through tankyrase 1 and positively regulated mitotic progression and telomere function and stability (Boehler et al., 2011). Recently, PARP3 was shown to act synergistically with PARP1 in DSB repair (Langelier et al., 2014).

Two other PARylating PARPs - tankyrase1 and tankyrase 2 were shown to be also involved in DSB repair. Tankyrases are well-known to regulate Wnt signalling and telomere function (Dodge and Lum, 2011; Huang et al., 2009) but were also shown to be involved in DSB break repair by regulating homologous recombination (Nagy et al., 2016).

3. The role of PARPs in establishing chromatin architecture and function

For timely response to critical changes in the cellular environment such as DNA damage, environmental signals of low energy or hormonal signalling, the chromatin needs to be reorganized locally to enable access to specific repair or transcription factors. PARP1 is able to orchestrate these changes to chromatin architecture and in turn chromatin function via a number of diverse but sometimes poorly understood mechanisms. These mechanisms include; PARP1 direct binding to chromatin independently of the underlying sequence or in a sequence-specific manner, PARP1 interacting partners and recruitment of co-factors via PAR chains – perhaps via PAR chain length and complexity (Kraus, 2008). Additionally, when associated to chromatin, PARP1 automodifies itself or it PARylates histones and other chromatin-associated factors including transcription factors thus altering chromatin structure (Pascal and Ellenberger 2015). It has been also shown that PARP1 binds transcriptional regulators and may bind directly promoters ((Krishnakumar et al., 2008) and reviewed in (Kraus, 2008)). The regulation of substrate selectivity and switch from automodification to PARylation of other factors remains largely obscure (Gibbs-Seymour et al., 2016). Intriguingly, recent report suggests that unmodified PARP1 compacts chromatin in a binding-mode of an architectural factor, demonstrating a non-DNA-damage related function for PARP1 (Muthurajan et al., 2014). Altogether, diverse modes of PARP1 binding to chromatin and the variation in the catalysed monomeric or polymeric, branched or unbranched

modifications provides multiple levels of complexity of ADP-ribosylation signalling on chromatin.

3.1. ADP-ribosylation, chromatin structure and transcription regulation

Chromatin structure alterations can directly be induced by PARP1 modifying the basic structural units of nucleosome – the histones. The first evidence that demonstrated a direct effect of PAR on chromatin structure was that locally generated PAR relaxed chromatin (Poirier et al., 1982). The linker histone H1 was identified as the major acceptor of PAR. Although PARylated chromatin looked like it was devoid of H1, the PARylated H1 stayed associated to chromatin (Poirier et al., 1982). In specific biological situations such as hormone treatment, over-activation of PARP1 caused H1 displacement from chromatin, making the chromatin more open and amenable for remodelling of progesterone-responsive regions (Wright and Beato, 2012). Furthermore, the nucleosome alone can be destabilized by PARylation of the core histones because of the polyanionic nature of the PAR polymer (Huletsky et al., 1989; Realini and Althaus, 1992). Conversely, Kim *et al.* suggested PARP1 binds core histones without modifying them but showed that the binding induced increase of nucleosomal repeat length (Kim et al., 2004). These and other studies confirmed that PARP1-mediated chromatin remodelling can induce activation and repression of gene transcription (Krishnakumar et al., 2008; Wright and Beato, 2012). Indeed, PARP1 has been proposed as a switch regulator between the activation and repressing complexes in transcription (Ji and Tulin, 2010; Kotova et al., 2010). Further to PARP1's suggested role in transcriptional repression, PARP1 has been implicated in heterochromatin or repressive chromatin formation, particularly rDNA regulation and nucleoli structure and also pericentric and centromeric heterochromatin formation (discussed in section 4.1.). *Drosophila's* puff loci are the most illustrative example of de-condensation of PAR-enriched chromatin. Upon heat-shock, PARylation accumulates at the 'puffing' loci and if PARP is depleted or inhibited, the nucleosomes do not collapse and consequently the *Hsp70* gene is not transcribed faster (Petesch and Lis, 2008; Tulin and Spradling, 2003).

Transcription factor and tumour suppressor p53 has a crucial role in DDR, particularly in determining the cell fate (Muller and Vousden, 2013). PARP1 catalytic activity alters the subcellular localization of p53 and positively regulates p53 transcriptional activity during DDR. In the absence of DNA damage, p53 is exported out of the nucleus and degraded by MDM2. Following DNA damage, a whole host of factors collaborate to relieve p53 of the antagonizing activities of MDM2, including PARylation by PARP1 which specifically blocks p53 interaction with the nuclear export factor CRM1 and the export of p53 into cytoplasm. Inhibited interaction of p53 and CRM1 forces p53 nuclear localization and favours activation of p53-dependent genes (Kanai et al., 2007).

PARP1 can modulate SIRT1 (sirtuin) transcriptional activity by depleting the pool of NAD⁺ co-factor necessary for SIRT1 deacetylase activity while PARP2 can directly affect SIRT1 promoter activity (reviewed in (Canto and Auwerx, 2011)). Reciprocally, SIRT1 can negatively regulate PARP1, both through regulation of

PARP1 transcription and by deacetylation of PARP1, further proving the complex relationship between PARPs and sirtuins (reviewed in (Canto et al., 2015)). The interplay between SIRT1 and PARPs on chromatin (and indeed in other cellular compartments) regulates metabolic signalling and defines metabolic homeostasis of a cell. MACROD1/2 and TARG1 proteins, by hydrolysing the SIRT1 product OAADPR, could also affect transcriptional and metabolic regulation (Chen et al., 2011; Peterson et al., 2011).

The role of PARP1 in transcription is very fast-moving and new targets are being identified constantly. Point of fact - the latest report shows that PARP1, through ADP-ribosylation of the protein complex NELF, positively regulates transcription by stimulating stalled PolII into elongation (Gibson et al., 2016).

3.1.1. ADP-ribosylation and histones

Histones were shown more than four decades ago to be ADP-ribosylated *in vivo* (Ueda et al., 1975) but the exact sites and the physiological consequences have not been clarified yet. An *in vitro* study showed that upon auto-modification PARP1 binds with high affinity to the non-nucleosomal H2A-H2B and H3-H4 complexes and histones (Muthurajan et al., 2014). PARylation of PARP1 but not histones, was shown to be a prerequisite for PARP1 histone chaperone and nucleosome assembly activity. Furthermore, newly identified HPF1/C4orf27 protein was shown to be mandatory for the switch from PARP1 automodification to PARP1-mediated histone ADP-ribosylation in DDR signalling (Gibbs-Seymour et al., 2016).

Macrodomain-containing histone variants were linked to ADP-ribosylation when it was shown that macroH2A1.1 binds ADP-ribose and PAR (Karras et al., 2005) and PARylated PARP1 (Timinszky et al., 2009). MacroH2A1.1 and PARP1 have shared functions and shared interactors on chromatin (Hussey et al., 2014). PELP1 is a transcriptional coactivator found to bind macrodomain of macroH2A proteins and PARP1. MacroH2A1 recruits PELP1 to promoters of macroH2A1-dependent genes and they cooperate to control gene expression (Hussey et al., 2014).

In HeLa cells macroH2A1.1 was required to recruit PARP1 to the promoter of the gene Hsp70.1 and for heat-shock induced activation of the locus (Ouararhni et al., 2006). Chen *et al.* demonstrated that macroH2A1.1 and macroH2A1.1-bound PARP1 recruited CBP to sustain H2B K12 and K1120 acetylation on activated and repressed genes (Chen et al., 2014). This acetylation is lost in cancer cells lacking macroH2A1.1 expression (Buschbeck et al., 2009; Chen et al., 2014). Noteworthy, macroH2A1.1 is one of the two splice variants generated by alternative splicing of a mutually exclusive exon (Pehrson and Fuji, 1998). While the other isoforms called macroH2A1.2 is predominantly expressed in proliferating cells, macroH2A1.1 is upregulated during differentiation (Creppe et al., 2012; Sporn and Jung, 2012). Whether this reflects a difference in the requirement of PARP1 recruitment and regulation in differentiating cells, remains to be addressed. In senescent cells senescence-associated genes are marked also by macroH2A1.1 and acetylation (Chen et al., 2015) and PARP1 has also been implicated in senescent phenotype (Ohanna et al., 2011). Moreover,

macroH2A1.1 and PARP1 cooperation is required for senescence-associated secretory phenotype (Chen et al., 2015). In *Drosophila*, another histone variant, H2Av histone variant (H2AX orthologue), co-localises with PARP1 at the stress-induced chromatin loci and this event has been suggested as crucial to positively regulate PARP1 enzymatic activity (Kotova et al., 2011).

The crosstalk between histone modifications and PARylation is poorly understood, but the crosstalk was reported on isolated histones. PARylation of the histone H3 prevented methylation of H3 by SET7/9 mono-methyltransferase and consequently H1 was methylated by SET7/9 (Kassner et al., 2013).

3.1.2. ADP-ribosylation and nuclear receptors.

With a well-documented role of PARP1 involvement in transcriptional regulation (Kraus and Hottiger, 2013) perhaps it is not surprising that PARP1 activity can also impact on many processes by regulating hormones and other types of nuclear receptors (NR). Briefly, hormones bind to NR – a superfamily of ligand-dependent receptors present inside the cell with the ability to bind DNA sequences directly and thus in turn affect the expression of surrounding genes. Subsequently NR, including estrogen receptor- α (ER α) and androgen receptor (AR) are also classed as transcription factors. How ADP-ribosylation can impact on this widespread family of receptors which affects nearly every aspect of biology is discussed next.

Estrogens and estrogen receptors ER α and ER β have key roles in both male and female biology which reach far beyond sexual development and reproductive health including but not limited to immunology, cardiology, neurobiology and tumorigenesis (Heldring et al., 2007; Thomas and Gustafsson, 2011). Importantly, PARP1 has been shown to interact and directly ADP-ribosylate ER α which resulted in increased ER α transactivation and up-regulation of estrogen responsive genes (Zhang et al., 2013). Additionally, AR the major male sex hormone receptor of which aberrant overexpression typically drives prostate cancer progression, has also been reported to be modulated by PARP1 (Schiewer et al., 2012). PARP1 promoted AR binding to chromatin and thus increased transcription of AR target genes (Schiewer et al., 2012).

PARP1 has also been reported to repress transactivation of NR. For example, PARP1 was demonstrated to block liver X receptor (LXR) mediated expression of ATP-binding cassette transporter A1 (ABCA1) in macrophages (Shrestha et al., 2016). Since LXR, *inter alia*, orchestrates macrophages-dependent removal of fatty deposits from arterial walls by cholesterol transport and elimination – and PARP1 attenuates this protective effect – PARP inhibitors may be useful in the treatment of atherosclerosis. However, it must first be taken into consideration that, another PARP enzyme, TIPARP (PARP7) has instead been demonstrated to mono-ADP-ribosylate and co-activate LXR (Bindesboll et al., 2016). Interestingly, the TIPARP activation of LXR could be reversed by increased expression of the mono(ADP-ribosyl) hydrolase MACROD1 indicating that regulation of NR by ADP-ribosylation has many layers and a range of responses. Indeed, PARP1 differentially regulates members of the obligate heterodimers retinoid X receptors (RXR) superfamily of receptors. On the one hand, PARP1 specifically

blocks RXR-thyroid hormone receptor heterodimers (by direct binding to RXR) (Miyamoto et al., 1999). But on the other hand PARP1-PPAR γ complexes facilitated the displacement of repressive elements at the chromatin and favoured increased expression of PPAR γ target genes (Lehmann et al., 2015).

As previously alluded to, in addition to PARylating enzymes, demodifying enzymes have also been implicated in NR regulation. Indeed, MACROD1 as well as repressing LXR has also been reported *in vitro* to act as an essential co-factor for ER α , AR and NF- κ B (Han et al., 2007; Wu et al., 2011; Yang et al., 2009). Furthermore, closely related protein MACROD2 may also have a role in ER α regulation as MACROD2 has been described as a mediator of estrogen-independent growth (Mohseni et al., 2014).

3.1.3. macroPARPs and transcriptional regulation

MacroPARPs proteins contain the ADP-ribose-binding macro domain that act as ADP-ribosylation sensor (Forst et al., 2013; Karras et al., 2005) and the ART domain. There are three macroPARPs: PARP9, PARP14 and PARP15 that differ in the number and type of ADP-ribosylation-binding modules and their PARP activity. PARP9 is predicted to be inactive due to non-conserved crucial catalytic residues. MacroPARPs were first discovered 15 years ago and named BAL (B-aggressive lymphoma) proteins as they were found overexpressed in high-risk diffuse large B-cell lymphoma patients (Aguiar et al., 2005; Aguiar et al., 2000). All three proteins contribute to transcriptional regulation in cells of the lymphoid lineage, but their more widespread expression suggest that they might have a role in other tissues (Aguiar et al., 2000; Hakme et al., 2008). MacroPARPs were shown to act as transcriptional repressors, but PARP9 was also reported to activate gene transcription (Aguiar et al., 2005; Juszczynski et al., 2006). PARP14 was additionally shown to switch from a repressor in unstimulated conditions to activator in IL-4-stimulated conditions (Goenka and Boothby, 2006; Mehrotra et al., 2011).

PARP14 was suggested to be a reader of PARP10 mono-ADP-ribosylation achieved through the two macrodomains (Forst et al., 2013). PARP14 cooperates with repressive deacetylases, but upon stimulation its ADP-ribosylating activity contributes to reorganizing the chromatin factors and activating transcription (Mehrotra et al., 2011). PARP14 was further shown to directly regulate pro-survival signalling and metabolic genes in lymphoma (Cho et al., 2011; Cho et al., 2009). PARP15 together with other PARPs was shown to regulate the integrity of stress granules in the cytoplasm whereby it contributes to the regulation of mRNA translation and stability (Leung et al., 2011).

3.1.4. PARP1 in regulation of pluripotency and differentiation

Reprogramming somatic cells into induced pluripotent stem cells (iPSC) presumes orchestrated action of many nuclear factors. PARP1 was identified as a strong potentiator of the OSKM (Oct4, Sox2, Klf-4 and c-Myc)-induced reprogramming of mouse embryonic fibroblasts (Doege et al., 2012). Reprogramming was compromised in *Parp*^{-/-} cells because PARP1 establishes early activating histone marks at pluripotency loci and in that way positively regulates their transcription and consequently characteristics of iPSC. Moreover,

accumulation of PARP1 in the iPSC pluripotency loci was not accompanied by the apoptosis-associated cleaving of PARP1, pointing out a non-DNA damage-related function of PARP1. PARP1 positive regulation of reprogramming was additionally credited to enhance exogenous Oct4 binding to the pluripotency loci even when other three nuclear factors were not introduced into the cells (Doege et al., 2012). Furthermore, Weber *et al.* showed that PARP1-dependent PARylation of Sox2 favoured Sox2 binding to *Fgf4* and *Fgf4* expression, factors crucial for initiation of reprogramming (Weber et al., 2013). It was also suggested that, in addition to PARP1, PARP7 localizes on several crucial pluripotency genes and that both proteins contribute to maintenance of active marks and therefore the developmental plasticity of the cells (Roper et al., 2014).

Transcription intermediary factor (TIF1 β) and Heterochromatin protein 1 (HP1 β) interact during endodermal differentiation to regulate the expression of endodermal-specific genes. Both PARP1 and PARP2 were found to bind HP1 β and TIF1 β and to regulate TIF1 β transcriptional activity. More specifically, PARP2 regulates primitive endodermal differentiation and PARP1 is involved in parietal (terminal) endodermal differentiation (Quenet et al., 2008). PARP2 regulates transcriptional activity of peroxisome proliferator-activated receptor- γ (PPAR γ), a key factor of white adipose tissue differentiation (Bai et al., 2007) and *Parp2* KO mice were shown to suffer from decreased adipocytes differentiation and function (Bai et al., 2007). In a preadipocytes cell line the interaction of Tet1/2 and PPAR γ was reported to induce PPAR-response elements (PPRE) 5C-hydroxymethylation during adipocyte differentiation (Fujiki et al., 2013). PARP inhibitor treatment affected PPAR γ and Tet1 interaction and consequently decreased 5C-hydroxymethylation around PPRE (Fujiki et al., 2013).

In neural stem cells, PARP1 phosphorylation-dependent PARylation of components of a repressor complex induced the dismissal of this repressive complex from promoters. Consequently, transcriptional activators could bind the promoters of genes important for neuronal differentiation and promote the differentiation (Ju et al., 2004).

4. The implication of ADP-ribosylation in chromatin remodelling

PARP1 is the most abundant chromatin protein after histones (Dantzer and Santoro, 2013) and even though it has been classically related with DNA damage events, a more general role in chromatin structure regulation is increasingly being appreciated. PARP1 has been implicated in chromatin remodelling thus regulating the underlying DNA sequence accessibility and transcriptional programmes. Main drivers of chromatin remodelling are ATP-dependent chromatin remodelers, in particular SNF2 family proteins and histone chaperones (reviewed in (Narlikar et al., 2013)). Wright and colleagues report that the ATP necessary for chromatin remodelling can be generated locally in the nucleus (Wright et al., 2016). They found that in breast cancer cells upon hormone stimulation, PAR is hydrolysed to ADP-ribose which is then converted into ATP by the action of the NUDIX5 enzyme. The locally generated ATP enables hormone-induced chromatin remodelling for activation of transcriptional programmes regulating cell proliferation.

Amplified-in-liver-cancer 1 (ALC1, also known as CHD1L) is a chromatin remodelling SNF2-like ATPase which is recruited to DNA-damage sites through its PAR-binding macrodomain (Ahel et al., 2009; Ahel et al., 2008; Gottschalk et al., 2009). It was reported that ALC1 is allosterically activated by PAR bound to PARP1 and that they cooperatively bind to nucleosomes to remodel them (Gottschalk et al., 2012). ALC1 interaction with PARP1 has been suggested to facilitate early reprogramming events (Jiang et al., 2015). Briefly, PARylated PARP1 was shown to interact with and recruit ALC1 to key pluripotency sites thus positively regulating the stemness of early reprogrammed cells.

The chromatin remodelling factor ISWI was also reported to be PARylated both *in vitro* and *in vivo* (Sala et al., 2008). The PARylation of ISWI in cells reduced its binding to chromatin, implying a negative role for PARylation in chromatin remodelling. SMARCA5/SNF2H, the catalytic subunit of the ISWI remodelling complex, interacts with E3 ubiquitin ligase RNF168 in a DNA damage- and PARP-dependent manner and activates RNF8/RNF168 ubiquitylation response (Smeenk et al., 2013). CHD4 (chromodomain helicase DNA-binding protein 4) is a component of the NuRD (Nucleosome Remodelling and Deacetylation) complex involved in cell type specific gene repression during differentiation (Fujita et al., 2004; Marfella and Imbalzano, 2007; Murawsky et al., 2001) and localisation of repair factors at sites of DSBs (Larsen et al., 2010). CHD4 recruitment to DNA damage sites was shown to be reliant on interaction with PAR (Polo et al., 2010). In *Drosophila*, the protein is called dMi-2 and it has been shown to mediate nucleosome remodelling on stress-induced sites upon environmental stress. Accordingly, dMi-2 has been shown to accumulate at heat-shock loci by binding to locally produced PAR and consequently, to positively regulate the heat-shock genes expression in dependence of the remodelling activity (Murawska et al., 2011).

FACT (Facilitates chromatin transcription) complex is a heterodimeric complex consisting of SSRP1 and Spt16 unit that enables nucleosome remodelling and thereby facilitate transcription elongation. Once the Spt16 subunit becomes PARylated, it no longer associates with the SSRP1 subunit, their association with the nucleosome is lost leading to transcription repression (Heo et al., 2008; Huang et al., 2006).

Brg1, also known as Smarca4, is a chromatin remodelling protein and a major regulator of cardiac growth and differentiation. Activated Brg1 exerts its mode of action by associating with PARP1 and histone deacetylase on the chromatin, resulting in increased upregulation of cardiac foetal genes. During embryogenesis Brg1 preserves foetal differentiation in cardiomyocytes contributing to healthy development. However, in adult tissue Brg1 is erroneously reactivated by cardiac stress which induces pathological changes in gene expression leading to diseased states (Hang et al., 2010).

Taken together, ADP-ribosylation emerges as an important transient event directing the chromatin remodelers to sites where local chromatin structure needs to be altered to adapt the transcriptional programme.

4.1. PARP members in heterochromatin formation

Chromatin regions like telomeres, centromeres and nucleoli with the rDNA exhibit special regulation of structure in order to tightly control levels of compaction. These regions are marked by specific PTMs, histone variants and other architectural factors.

ADP-ribosylation regulating telomeres function

Telomeres are protective structures at the end of chromosomes composed of shelterin proteins. Telomeric repeat-binding factor 1 (TRF1) is a member of shelterin complex involved in telomeric homeostasis, while TRF2 protects chromosomal ends by stabilizing the t-loop (extended telomeric DNA with a single-stranded 3'-overhang). Both PARP1 and PARP2 were found to interact with TRF2 and to affect telomeres, though the evidence existing for this is controversial. For PARP1, reports show no implication or positive regulation of telomere length (Beneke et al., 2008; d'Adda di Fagagna et al., 1999; Espejel et al., 2004; Samper et al., 2001; Tong et al., 2001). PARP2 on the other hand regulates DNA-binding activity of TRF2 and enables repair when necessary (Dantzer et al., 2004). Additional regulation of telomere functions is brought into play by the tankyrases. Tankyrase 1 binds and PARylates TRF1 thereby inhibiting its binding to telomeres. When TRF1 is not present at telomeres, telomerase access the telomeres and increases their length (Ancelin et al., 2002; Hsiao and Smith, 2008; Smith et al., 1998; van Steensel and de Lange, 1997). Plk1 kinase, responsible for G2-M transition, centrosome and spindle function, was further shown to positively regulate tankyrase 1 stability and activity. In the case of aberrant Plk1 activity and no tankyrase 1 activity, telomeric fusions arise and are followed by aberrant spindle pole assembly (Ha et al., 2012).

ADP-ribosylation regulating centromeres

Centromeres are specialized chromatin regions essential for chromosome segregation and their function is dependent on the local chromatin structure and not the underlying sequence. Centromere protein A and B (CENPA, CENPB) and the mitotic spindle checkpoint protein BUB3 nucleate centromeric heterochromatin (Nakagawa et al., 2002) and interact with PARP1 and PARP2 (Saxena et al., 2002a; Saxena et al., 2002b). But while PARP1 localizes to centromeric and pericentric chromatin, covering minor and major satellites, PARP2 probably covers only minor satellites in the outer centromeric regions. Both PARP1 and PARP2 were also identified as partners of the pericentric proteins TIP1 β and HP1 (Quenet et al., 2008).

rDNA, nucleoli and CTCF elements

Ribosomal genes exist as multi-copy repeat clusters that are spatially organized on the surface of the nucleoli. A proportion of the rDNA repeat units are silent and form a type of heterochromatin that is replicated in the mid/late S phase (Guetg and Santoro, 2012; Santoro, 2011; Santoro et al., 2002) PARP1 binds to rDNA after replication and through PARylation of the silent rDNA chromatin, establishes rDNA heterochromatin (Guetg et al., 2012).

MeCP2 is the founding member of the methyl CpG binding domain (MBD)-containing family whose role is to silence gene expression by aggregation of

pericentric chromatin (Jones et al., 1998; Nan et al., 1997). MeCP2 was recently demonstrated to be PARylated and this modification lead to decreased clustering of pericentric chromatin, while PARP1 depletion increased the aggregation (Becker et al., 2016). It was suggested by the authors that the extent of PARylation on MeCP2 influences its DNA binding affinity and in this way interferes with the clustering.

CTCF, a boundary element with a recognised role in activating and repressing transcription, was shown to move to the nucleoli in terminally differentiated mammalian cells (Torrano et al., 2006) and to be enriched on rDNA genes (van de Nobelen et al., 2010). In *Drosophila* the disruption of CTCF causes aberrant nucleoli structure and rDNA expression and PARP or PARG disruption partly phenocopies CTCF mutants (Guerrero and Maggert, 2011). Specifically, *Drosophila Parp* mutations lead to incorrect localisation of nucleolar-specific proteins to nucleoli and that consequently affects nucleolar assembly and ribosomal biogenesis (Boamah et al., 2012). *Drosophila* insulator-binding proteins CTCF, Su(Hw), Mod(mdg4)2.2 and centrosomal protein 190 (CP190) were shown to be PARylated and *Parp* mutations lead to aberrant insulator activity (Ong et al., 2013).

In details, site-specific PARylation at CP190 was shown to promote intrachromosomal interactions between distant insulator sites and with nuclear lamina, subsequently affecting the 3D architecture of the genome. CTCF-PARP1 interaction was also reported to regulate circadian genes transcription in an oscillating manner by recruiting the circadian loci to repressive nuclear lamina regions (Zhao et al., 2015). In this way a rhythmic and reversible attenuation of circadian genes transcription is achieved.

4.2. PARylation controlling key biological processes in *Drosophila*

Drosophila PARP1 orthologue was suggested to be largely involved in nucleoli heterochromatin (where it heavily PARylates diverse substrates) and maintenance of copia sequences. When *Parp* was deleted in *Drosophila*, half of the mutants were arrested at a specific larval stage, implicating that PARP1 might have functions for larval development as well (Ji and Tulin, 2010; Tulin et al., 2002). Ecdysone is a hormone important for the onset of metamorphosis (Fletcher and Thummel, 1995). PARP1 enzymatic activity localizes to ecdysone-inducible loci, probably through the interaction with ecdysone receptor, and locally loosens the chromatin (Tulin and Spradling, 2003).

Gagne and colleagues reported that heterogenous nuclear ribonucleoproteins are PAR-binding proteins (Gagne et al., 2003). It took five more years to uncover that the alternative splicing factor/splicing factor 2 (ASF/SF2) also binds PAR (Malanga et al., 2008). In *Drosophila*, two ribonucleoproteins were shown to bind PAR and it was further demonstrated that this binding inhibits binding of ribonucleoproteins to RNA and thereby modulates RNA splicing pathways (Ji and Tulin, 2009).

5. Clinical exploitation of ADP-ribosylation

After decades of intensive research on PARP1 inhibition effects in cancer cell and *in vivo* models and promising results in preclinical stage, PARP inhibitors are

now in phase III clinical trials (for inhibitors overview see (Puigvert et al., 2016)). PARP inhibitors are either used in cells with defective homologous recombination repair or in combination with other DNA-damaging agents, taking advantage of the insufficient or inadequate repair which in combination with PARP inhibitors inevitably leads to cell death (Curtin and Szabo, 2013). Moreover, since in the absence of DNA damage PARP1 was shown to have a major role in modulating chromatin structure and transcriptional events associated with human diseases, translation of PARP inhibitors from chromatin into clinic becomes even more imperative (Feng et al., 2015).

PARP inhibitors are specifically being used for the treatment of breast and ovarian cancers with BRCA mutations. The PARP inhibitor olaparib has just been approved for advanced ovarian cancers with germline BRCA mutation (Feng et al., 2015). Additionally PARP inhibitors are being exploited to treat metastatic prostate cancer (Mateo et al., 2015). In a murine model of metastatic melanoma PARP1 inhibition has led to decreased metastatic potential (Rodriguez et al., 2013). Next to PARP1, the tankyrases in colorectal cancer and PARP14 in aggressive diffuse B-cell lymphoma, are also being tested as targets of inhibition in anti-cancer therapy (Huang et al., 2009; Iansante et al., 2015). Data on PARP inhibitors and their use in clinic has been summarised elsewhere (Curtin and Szabo, 2013).

p53 protein affects DNA repair, transcription and replication by binding and enhancing the activity of topoisomerase I and regulating DNA breaks (Albor et al., 1998; Gobert et al., 1999; Soe and Grosse, 2003). PARP1 was shown to PARylate topoisomerase I (Bauer et al., 2001; Ferro et al., 1983; Yung et al., 2004) and to antagonize p53-stimulated topoisomerase I-dependent recombination (Baumann et al., 2006). When topoisomerase is inhibited, an increase of DSB can occur and when DNA damage is extensive, the cells are forced into cell death. The increased sensitivity of the cells when both inhibitors are used is currently being tested for the use in clinic (Ray Chaudhuri et al., 2012) and reviewed in (Xu and Her, 2015).

MACROD1 was found overexpressed in lung, breast and colon cancer (Shao et al., 2015; Xi et al., 2010; Zhao et al., 2010) and associated with poorer prognosis. MACROD2 was shown to activate the protein kinase GSK3b by removing the inhibitory ADP-ribosylation (Rosenthal et al., 2013) and just like MACROD1, it is implicated in cancer (Gao et al., 2015; Mohseni et al., 2014). MACROD2 has further been implicated in aggressive phenotype of breast cancer: MACROD2 increased co-factor p300 binding to estrogen response elements in a subset of ER regulated genes, perhaps driving a more aggressive cancer phenotype as MACROD2 amplification was associated with poorer prognosis.

ALC1/CHD1L protein was found to negatively correlate with liver development and hepatocellular carcinoma tumour differentiation. ALC1 probably acts by opening the chromatin and inducing transcriptional programmes that drive the cells toward ancestral-like state with higher tumour malignancy potential. Importantly, inhibiting ALC1 makes the cells sensitive to small molecule inhibitor sorafenib (Liu et al., 2016). Transgenic expression of ALC1 in mice was

reported to cause tumours in several tissues including abdominal wall, neck, face, uterus and others, bringing further support to targeting ALC1 in cancer (Chen et al., 2009).

Regarding non-oncogenic ailments including stroke, traumatic brain injury, acute myocardial infarction and circulatory shock, the use of PARP1 inhibitors has proven encouraging in preclinical phases of research (reviewed in (Curtin and Szabo, 2013)). Regarding inflammation, auto-PARylation of PARP1 stimulates NF- κ B binding to DNA and fosters NF- κ B-dependent gene expression leading to boosted inflammatory response ((Chang and Alvarez-Gonzalez, 2001) and reviewed in (Feng et al., 2015; Mangerich and Burkle, 2012)). The exaggerated proinflammatory signalling might be relevant in cancer and other auto-immune conditions (Rosado et al., 2013) supporting the strategy of PARP suppression in cancer further.

6. Future perspectives

It took more than 50 years of extensive studies of PARP1 to finally discover and start taking advantage of it in clinical practice. There are 16 more human PARPs and many more de-ADP-ribosylating enzymes whose function still remain unclear or has not been put into use in clinic. Additionally, each factor involved in ADP-ribosylation has numerous interactors that also might be only vaguely explored. Indeed, ADP-ribosylation signalling regulating transcription and chromatin remains more obscure than revealed. Still, recent progress in the use of PARP inhibitors in clinics provides evidence that ADP-ribosylation is an important target. All things considered, ADP-ribosylation serves as an integration point on chromatin to attract, accumulate and expel specific factors in order to reorganize chromatin accordingly. With the advancement of mass spec technology and sequencing techniques the future studies on ADP-ribosylation cycle will be more comprehensive and detailed creating new opportunities for therapeutical design.

FIGURE

Figure 1. ADP-ribosylation as integration point of signalling on chromatin leading to spatio-temporal fine-tuning of gene expression in newly established situations.

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