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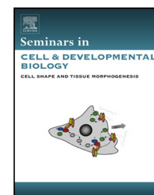

Review

PARP, transcription and chromatin modeling

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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 pictures 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.

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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, dobule-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-κB, 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, gltuamate and leucine rich protein 1; PcG, polycomb group bodies; Plk1, polo like kinase 1; PolII, Polymerase II; PPARγ, peroxisome proliferator-activated receptor−γ; PPRE, PPARγ 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, supressor 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.

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1. Introduction

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 [182]. 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 [26]. The amino acids accepting the modifications are most commonly glutamate, aspartate and arginine, but some other amino acids have been also reported as acceptors [12,150,183]. A major family of enzymes that generates ADP-ribosylation are poly-ADP-ribose-polymerases (PARPs) [161]. 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 [38]. Since PAR chain forms a helicoidal secondary structure that is similar to RNA and DNA, PAR can be considered as the third nucleic acid [38]. 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 [134]. 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 [9,12,25,41,56,71]). 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 milleu facilitating the adaptation of the cell to new situation (Fig. 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).

1.2.1. 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 [7,20]. 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 [170]. 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 summarised recently elsewhere and will not be discussed here [12,170,183]. 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 [85].

1.2.2. 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 [140,143]) and macrodomain containing proteins such as ALC1 and macroH2A [3,96,173] 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 [137], PBZ [4], WWE [184] and OB fold [194] (reviewed in [13,56,85,87]).

1.2.3. 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) [11,78,118,149,163,165]. 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 [170]. The by-product of sirtuin enzymatic activity, *O*-acetyl-ADP-ribose (*O*AADPR), can also be hydrolysed by MACROD1/D2 and TARG1 [28,135]. Other families of proteins that may remove the protein ADP-ribosylation are nucleoside diphosphate linked to another moiety X proteins (NUDIX) [132] and ectonucleotide pyrophosphatase/phosphodiesterases (ENPP/NPP) [131].

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 [44]. Following genotoxic insult PARP1 and PARP2 sense DNA damage by binding to the broken DNA ends and are specifically and

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