Seminars in Cell & Developmental Biology 63 (2017) 123–134

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

PARP1 orchestrates epigenetic events setting up chromatin domains

Fabio Ciccarone[a], Michele Zampieri[b,c,1], Paola Caiafa[b,c,*,1]

[a] Department of Biology, Faculty of Mathematics, Physics and Natural Sciences, University of Rome 'Tor Vergata', Rome, Italy
[b] Department of Cellular Biotechnologies and Haematology, Faculty of Pharmacy and Medicine, 'Sapienza' University of Rome, Rome, Italy
[c] Pasteur Institute-Cenci Bolognetti Foundation, Rome, Italy

ARTICLE INFO

Article history:
Received 21 June 2016
Received in revised form 5 October 2016
Accepted 24 November 2016
Available online 28 November 2016

Keywords:
Epigenetic regulation
Chromatin
PARylation
PARP1
DNA methylation
DNA hydroxymethylation
Histone methylation
Histone acetylation

ABSTRACT

Epigenetic events include reversible modifications of DNA and histone tails driving chromatin organization and thus transcription. The epigenetic regulation is a highly integrated process underlying the plasticity of the genomic information both in the context of complex physiological and pathological processes. The global regulatory aspects of epigenetic events are largely unknown. PARylation and PARP1 are recently emerging as multi-level regulatory effectors that modulate the topology of chromatin by orchestrating very different processes. This review focuses in particular on the role of PARP1 in epigenetics, trying to build a comprehensive perspective of its involvement in the regulation of epigenetic modifications of histones and DNA, contextualizing it in the global organization of chromatin domains in the nucleus.

Contents

Abbreviations: ARH3, ADP-ribosyl hydrolase 3; ARTD, ADP-ribosyltransferases diphtheria toxin-like; BRCA1, breast cancer type 1 susceptibility protein; CBP, CREB-binding protein; CCDN1, cyclin-dependent kinase 2; CTCF, CCCTC-binding factor; DMR1, differentially methylated region 1; E2F4, E2F transcription factor 4; ELK1, ETS transcription factor; ERK2, mitogen-activated protein kinase 1; EZH2, enhancer of zeste homolog 2; HP1, heterochromatin protein 1; IL-6, interleukin 6; ITPR1, inositol 1,4,5-trisphosphate receptor type 1; KDM4D, lysine (K)-specific demethylase 4D; KDM5B, lysine (K)-specific demethylase 5B; Ku70, Ku autoantigen 70 kDa; Macro D1/D2, macro domain containing protein 1/2; MDa, megadalton; MeCP2, methyl CpG binding protein 2; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NuA4, nucleosome acetylating H4 complex; p16, cyclin-dependent kinase inhibitor 2A; PCAF, P300/CBP-associated factor; Pol2, RNA polymerase 2; PPARγ, peroxisome proliferator-activated receptor gamma; rDNA, ribosomal DNA; SCN1A, sodium channel voltage gated type I alpha subunit; SET1/7/9, SET domain containing (lysine methyltransferase) 1/7/9; SIRT1, silent mating type information regulation 2 homolog 1; SNAI1, snail family zinc finger 1; SUZ12, suppressor of zeste 12 protein homolog; TARG1, terminal ADP-Ribose protein glycohydrolase; THBD, thrombomodulin; TSS, transcription start site; UHRF1, ubiquitin-like containing PHD and RING finger domains 1; α-SMA, alpha-smooth muscle actin.

* Corresponding author at: Paola Caiafa, Department of Cellular Biotechnologies and Haematology, Faculty of Pharmacy and Medicine, 'Sapienza' University of Rome, Viale Regina Elena 324, 00161 Rome, Italy.
E-mail address: caiafa@bce.uniroma1.it (P. Caiafa).
[1] Shared senior authorship.

http://dx.doi.org/10.1016/j.semcdb.2016.11.010

1. Introduction

Poly(ADP-ribosyl)ation (PARylation) is a post-translational modification catalysed by enzymes of the poly(ADP-ribose) polymerase (PARP) family, also known as the ADP-ribosyltransferase diphtheria toxin-like (ARTD) family due to its similarities in enzymatic features with ADP-ribosylating bacterial toxins. Consistently, the active enzymes of this family catalyse the transfer of ADP-ribose moieties from NAD^+ to specific amino acids including glutamate, aspartate and lysine residues [1,2]. Most of the members have mono-ADP ribosylating activity, while the enzymes properly named PARPs share polymerization activity. In fact, PARPs have the ability to further catalyse the elongation of a protein-mono(ADP-ribose) substrate into a poly(ADP-ribose) (PAR) branched chain [3] (Fig. 1).

Throughout the years, much attention has been focused on the PARP1 enzyme, as it is responsible for producing most of PAR in the nucleus. PARP1 is a pleiotropic enzyme involved in disparate functions including multiple pathways of DNA-damage response, gene expression and cellular signalling. The multitasking roles of PARP1 mirror, and at the same time can be explained by, the complexity of its structure and of the PARylation reaction itself. Human PARP1 is a 113 KDa multi-domain protein characterized by at least three main functional domains. The C-terminal catalytic domain (CD) is responsible for the enzymatic activity and contains the NAD^+-binding motif, known as "PARP signature". The N-terminal domain is considered the DNA-binding domain (DBD) as it contains the two zinc fingers (Zn1 and Zn2) responsible for the binding with specific DNA structures [2,4]. A third Zn-domain, structurally different from Zn1 and Zn2, mediates the DNA-dependent activation and the chromatin compaction functions of PARP1 [5]. The central domain contains the BRCA1 C-terminal (BRCT) domain, involved in protein-protein interaction, and the tryptophan-glycine-arginine-rich (WGR) domain that is responsible for PARP1 catalytic activation [5]. Notably, the central domain of PARP1 is historically considered the auto-modification domain (AD). In fact, the primary target of the PARylation is PARP1 itself and this auto-modification event contributes to its functional multiplicity [2,4]. Major auto-modification sites in the AD lie in the flexible loop connecting the BRCT and WGR domains. However, recent evidence extends auto-modification to the DBD and CD domains [6].

The functions of PARP1 pertain to both activity-independent actions associated to its unmodified isoform and activity-dependent actions mainly involving auto-modification. Unmodified PARP1 and basal PARP1 activity are involved in the coordination of housekeeping functions including transcriptional regulation and the control of telomeres and centromeres stability. Conversely, other signalling networks entail high PARP1 activity triggered by various *stimuli*, among which the DNA strand breaks are so far the best characterized. In particular, PARP1 acts as a primary "DNA nick sensor" that physically recognizes DNA lesions to elicit the intervention of several DNA-damage response pathways. Recognition of DNA breaks is followed by PARP1 activation and auto-modification [2]. *In vitro* activation of PARP1 by nicked DNA generates PAR of more than 200 ADP-ribose units in length with potential branching sites every 20–25 units. PAR modifications on PARP1 have been suggested to form a sort of matrix that assists the assemblage of the DNA repair effectors [7] (Fig. 1). Nuclear PAR degradation is mostly due to the Poly(ADP-ribose) glycohydrolase (PARG) enzyme activity, which performs both the *exo*- and *endo*-glycohydrolase cleavage of PAR until the last protein-proximal mono-ADP-ribose remains. This latter is then removed by the recently discovered proteins Terminal ADP-Ribose protein glycohydrolase (TARG1/C6orf130) and Macro Domain Containing Protein 1/2 (Macro-D1 and Macro-D2). Another PAR-degrading enzyme is the ADP-ribosyl hydrolase 3 (ARH3), which mainly shows mitochondrial and cytosolic localization [8] (Fig. 1).

In undamaged cells, PARP1 is present in three main biochemical states, as identified by sucrose gradient fractionation experiments. About 44% of total PARP1 consists of single molecules or homo-dimers showing low molecular mass. These isoforms are non-PARylated and refractory to activation by nicked DNA *in vitro*. In contrast, the multi-molecular complexes of about 0.7 and 1 MDa (10% and 35% of PARP1 molecules, respectively) include PARP1 isoforms with high basal activity and with reactivity towards nicked DNA [9]. Therefore, in basal conditions about a half of PARP1 molecules are catalytically active, which can be justified by the fact that several proteins and types of DNA structures can stimulate PARP1 activity in the absence of DNA damage [4] (See the Graphical Abstract). Interestingly, mass spectrometry analysis of the 0.7 MDa fraction revealed the NuA4 histone acetyltransferase complex as both PARP1 partner and activator. The remaining half part of PARP1 molecules are probably kept inactive and resistant to activation by a tight regulative control mediated by post-translational modifications, which might turn off/on PARP activity *in vivo* [9]. These mechanisms might be necessary to avoid useless and detrimental depletion of NAD^+, which is known to affect cell viability, and to allow a signal-regulated PARP1 activation, as exemplified by PARP1 methylation in the context of DNA-damage response [10].

Besides the auto-modification mechanism, PARP1 PARylates covalently several target proteins (heteromodification) thereby modulating their functions. Moreover, PAR can interact non-covalently with target proteins bringing specific PAR-binding motifs thus adding further complexity to PARylation reactions [3,4,8,11] (Fig. 1). In fact, the non-covalent PARylation extends the number of PARP1 partners and enables automodified-PARP1 to act as a nucleating factor for the formation of macromolecular complexes.

One of the most interesting and extensively investigated functions of PARP1 is the regulation of gene expression through the direct control of histone dynamics as well as through the coordination of epigenetic modifications. This review will focus on the multiple mechanisms that PARP1 and PARylation use for orchestrating specific histone and DNA modifications responsible for chromatin dynamics.

2. PARP1 and chromatin structure

Initial evidence of a role of PARP1 in the regulation of chromatin structure derives from pioneering studies reporting that PARylation of nucleosomes causes chromatin decondensation *in vitro* [12]. From a biochemical standpoint, it is reasonable to assume that the addition of highly negatively charged PAR onto chromatin proteins causes a sort of repulsion with DNA thereby inducing chromatin decondensation. Later *in vitro* evidence has emerged showing that the histone core of nucleosomes (H2A, H2B, H3 and H4) as well as the linker histone H1 are targets of PARylation by PARP1 and this event can elicit local decondensation of chromatin [13,14]. Actually, the interplay between PARP1, PARylation and histones is even more sophisticated. Much information comes from studies on *Drosophila melanogaster* where only one PARP enzyme, showing high homology with mammalian PARP1, is present. In particular, these observations indicate that disassembled H3 and H4 histones bind the CD of PARP1 and that H4 strongly induces PARylation *in vitro*. In contrast, H2B and especially H2A inhibit PARP1 activity. The inhibition by H2A may explain why H4-mediated PARP activation is unnoticeable when histones were assembled into nucleosomes [15]. It is noteworthy that several events modulating PARP1 action in chromatin specifically involve H2A histone variants and post-translational modifications. Nucleosomes containing