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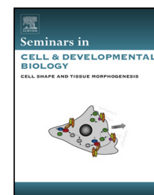

Review

PARP1 orchestrates epigenetic events setting up chromatin domains

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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.

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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.

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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

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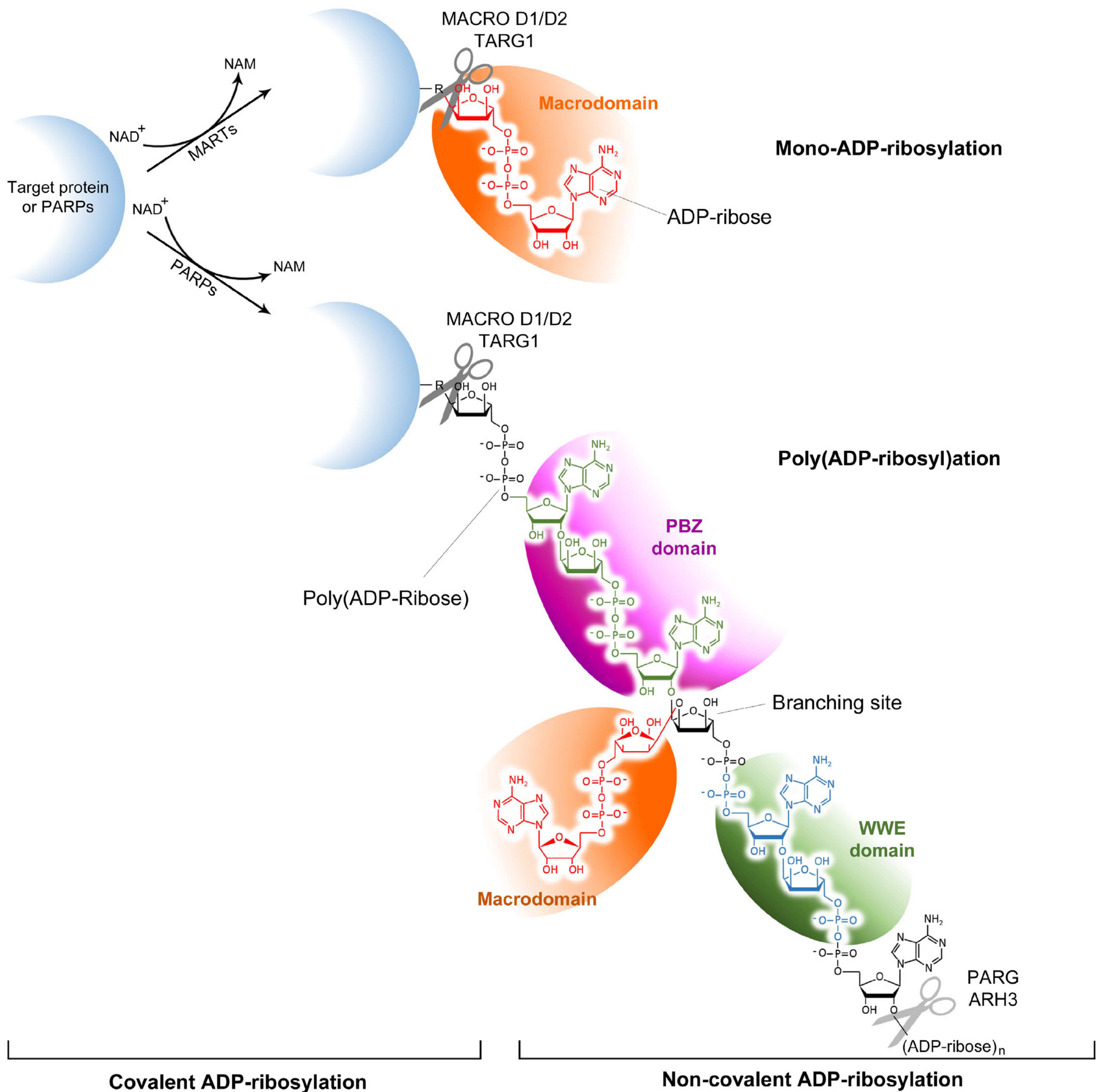

Fig. 1. PARP-dependent ADP-Ribosylation. Proteins and PARPs themselves are covalently ADP-ribosylated by using NAD^+ as ADP-ribose donor, releasing nicotinamide mononucleotide (NAM). Specific PARPs can ADP-ribosylate previous mono-ADP-ribosylated proteins resulting in the formation of a long and branched poly(ADP-ribose) polymer (PAR). Different protein domains recognize and bind non-covalently mono-ADP-ribose or poly(ADP-ribose). The Macrodomain recognition parts of PAR are indicated in red. The WWE domain recognition part of PAR is indicated in blue. The PBZ domain recognition part of PAR is indicated in green. PARG degrades PAR by performing either *exo*- or *endo*-glycosylase activities, leaving mono-ADP-ribosylated proteins. Mono-ADP-ribosylated proteins can be substrate of TARG1 or Macro D1/D2 proteins, which can remove the last protein-bound ADP-ribose unit.

histone variant H2Av (*Drosophila* homolog of the mammalian H2AZ/H2AX variants) are associated with PARP1 in specific promoters. The phosphorylation of H2Av, mediated by external *stimuli* (*e.g.* irradiation), favours the interaction between PARP1 and H4 thereby triggering PARylation [16]. Similarly, acetylation of H2A lysine 5 stimulates PARP1 activity at specific chromatin *loci* in response to heat shock, possibly masking the inhibition by H2A and/or triggering the activation by H4 [17]. Another H2A histone variant showing functional association with PARP1 is the macroH2A.1, which interacts with mono- and poly(ADP-ribose) through a large C-terminal domain known as macrodomain. MacroH2A.1 is able to inhibit the activity of PARP1 thereby maintaining the heterochromatic state of the inactive X chromosome and the repression of some inducible genes [18,19]. Moreover, macroH2A.1 favours the acetylation of H2B by recruiting PARP1 onto positively regulated genes [20].

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The ability of PARP1 to regulate chromatin structure extends well beyond PARylation. Strikingly, unmodified PARP1 drives condensation of chromatin by assembling nucleosomes in a way similar to that of H1 histone. Consistently, in the absence of NAD^+, PARP1 promotes chromatin compaction as revealed by its capability to protect the linker DNA between nucleosomes from nuclease digestion *in vitro* [21]. Recent biochemical studies *in vitro* indicate that unmodified PARP1 binds strongly to mononucleosomes containing symmetric linker DNA [22]. PARP1 interaction with trinucleosomes, a minimal model of native chromatin *in vitro*, instead occurs in the absence of extranucleosomal linker DNA, which is consistent with its role as chromatin architectural protein [23]. On the other hand, the activation of PARP1 mediated by stimulatory events (*e.g.* DNA damage, transcription) induces local chromatin decondensation reducing its affinity for it. In this context, automodified PARP1 may also have a histone chaperone function because it facilitates the reassembling of free histones into nucleosomes *in vitro* [23].

The interaction of unmodified PARP1 with nucleosomes resembles that of histone H1, which is able to bind the entry/exit sites of linker DNA at the surface of nucleosomes to compact chromatin. Similarly, a single PARP1 molecule is able to wrap up the nucleosome through the interaction of its Zn1 and Zn2 with the linker DNA at both its exits from the histone octamer [22]. In spite of these similarities, PARP1 and H1 show non-overlapping distribution on the *Drosophila* salivary gland polytene chromosomes. In fact, PARP1 is preferentially associated with less condensed chromatin while H1 mainly co-localizes with highly condensed chromatin [21]. This peculiar distribution of H1 *vs.* PARP1 indicates that, even though they are both associated with silent chromatin, their role may be different. PARP1 is associated with less condensed chromatin domains that can be further decondensed to permit transcription after PARP1 activation.

Besides its typical structural participation in forming constitutive heterochromatin, H1 plays similar functions in specific gene promoters as a mechanism of transcriptional repression. This kind of behaviour occurs on a subset of PARP1-stimulated promoters where the presence of PARP1 or H1 relates to transcriptional activity. PARP1 is located near the transcription start site (TSS) of active genes where it acts excluding H1 [24]. Notably, the exclusion of H1 from PARP1-regulated genes can be independent (*e.g. SCN1A* and *ITPR1*) [24] or dependent (*e.g. CCDN1*) on PARylation [25]. Consistently, PARP1 promotes the transcription of hormone-regulated genes through the displacement of H1 as part of the progestin pathway, which triggers the CDK2-mediated phosphorylation and subsequent activation of PARP1 [26].

2.1. PARP1 in the control of histone epigenetic modifications

Histone acetylation

Histones undergo covalent modification at conserved lysines by a class of enzymes called histone acetyltransferases (HATs). Acetyl groups remove positive charges reducing the affinity of histones for DNA thereby providing RNA polymerase 2 (Pol2) and transcription factors with access to promoters. Consistently, histone acetylation is typically associated with activation of genes while deacetylation, mediated by histone deacetylases (HDAC), represses transcription.

The first indication of a relationship between histone acetylation and PARylation dates back to more than thirty years ago suggesting their cooperation in the maintenance of accessible chromatin and transcription [27]. However, the underlying mechanisms have only become known recently.

An indirect link between PARylation and H3/H4 acetylation has been observed at the foot of the signalling cascade of ERK2, whose phosphorylation allows the binding and activation of PARP1 independently of DNA damage. This interaction favours the ERK2-mediated phosphorylation of ELK1, which activates target genes possibly by increasing histone acetylation [28].

A number of studies report hypoacetylation events, both global and *locus*-specific, upon down-regulation of PARylation [9,20,29]. Among the possible causes, derepression of deacetylase activity has been suggested [29,30]. In this context, PARylation-mediated inhibition of SIRT1, the first known mammalian member of the Sirtuins family, has been widely demonstrated. SIRT1 is a NAD^+-dependent deacetylase that regulates diverse aspects of global metabolism by modulating the acetylation state of several metabolic enzymes and transcriptional regulators. SIRT1 also mediates histone deacetylation with preference for H1 lysine 26, H4 lysine 16, and H3 lysine 9 [31]. The inhibition of SIRT1 by PARP1 mainly occurs in a competitive manner due to the higher affinity of PARP1 for their common substrate NAD^+ [32]. On the other side, SIRT1-dependent deacetylation of PARP1 restrains its enzymatic activity under stress conditions [32]. In addition, there is evidence that PARP1 interacts with HDAC enzymes (*e.g.* HDAC1, 2 and 3) but its implication on deacetylation remains undetermined [33].

An additional link between PARylation and acetylation might exist *via* the positive transcriptional control by PARP1 of the histone acetyltransferases p300, PCAF and CBP [29,30] together with the recently identified covalent PARylation of HDAC4, P300 and CBP [30]. Concerning the last of them, PARP1 is required for the CBP-mediated acetylation of H2B on macroH2A1.1-target genes [20]. Notably, PARP1 is itself a target from acetylation that is a key event necessary for activation of NF-κB-dependent genes [33].

Furthermore an interesting target site conflict could occur directly on histone molecules as both acetylation and PARylation compete for the same lysine. Indeed is has been demonstrated that lysine H4 lysine 16 acetylation impairs the PARylation of the histone H4 [13].

Histone methylation

While histone acetylation is mainly associated with active transcription whatever the modified residue is, the epigenetic meaning of histone methylation is quite complex. In fact, methylation of different lysine residues may have different, sometimes opposing, effects also depending on the degree of methylation (mono-, di-, or tri-methylation). Moreover, histones can also be methylated on arginine residues. Enzymes that add or remove the methyl group, known as lysine methyltransferases-KMTs and lysine demethylases-KDMs, respectively, establish the lysine methylation states of histones.

H3 lysine 4 methylation

One of the first histone methyl marks that was characterized in detail is the methylation of histone H3 at lysine 4 (H3K4me). All three methylation states of histone H3K4 are generally associated with euchromatic regions and then active transcription. In particular, H3K4me2/me3 are highly enriched at the TSS of active genes in association with Pol2 and acetylated histones. H3K4me1 is instead typical of enhancers [34]. Notably, a strong positive correlation between PARP1 and H3K4me3 concerns several promoters genome-wide. PARylation has an important role in the maintenance of H3K4me3 as it impinges on its demethylation process through the covalent modification of the demethylase KDM5B. PARylation impairs KDM5B activity and its binding to histone H3 *in vitro*. Consistently, an increased level of KDM5B at TSS of active genes is associated with decreased H3K4me3 after inhibition of PARylation *in vivo*. However, these changes do not necessarily affect transcription while PARP1 knocked-down does because of reduced H3K4me3 and loading of H1 as well. This would indicate that the action of PARP1 on KDM5B is less relevant for transcriptional regulation than the PARP1-H1 antagonism. However, after depletion of both PARP1 and KDM5B, H1 failed to localize at TSS suggesting that KDM5B is required for the H1-mediated transcriptional repression also when PARP1 is absent. Therefore, PARP1 positively

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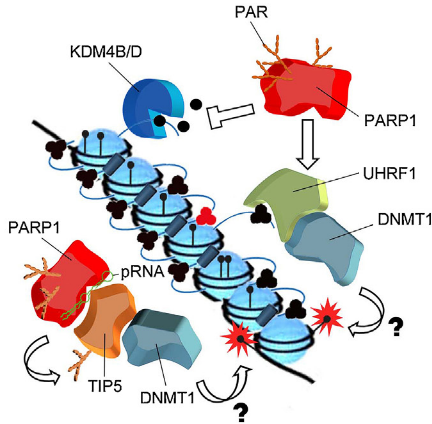

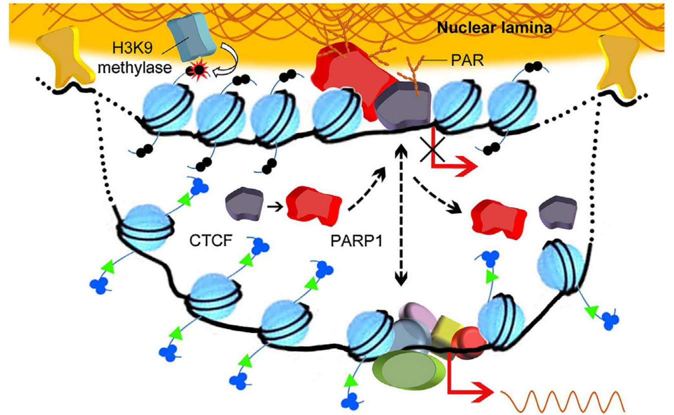

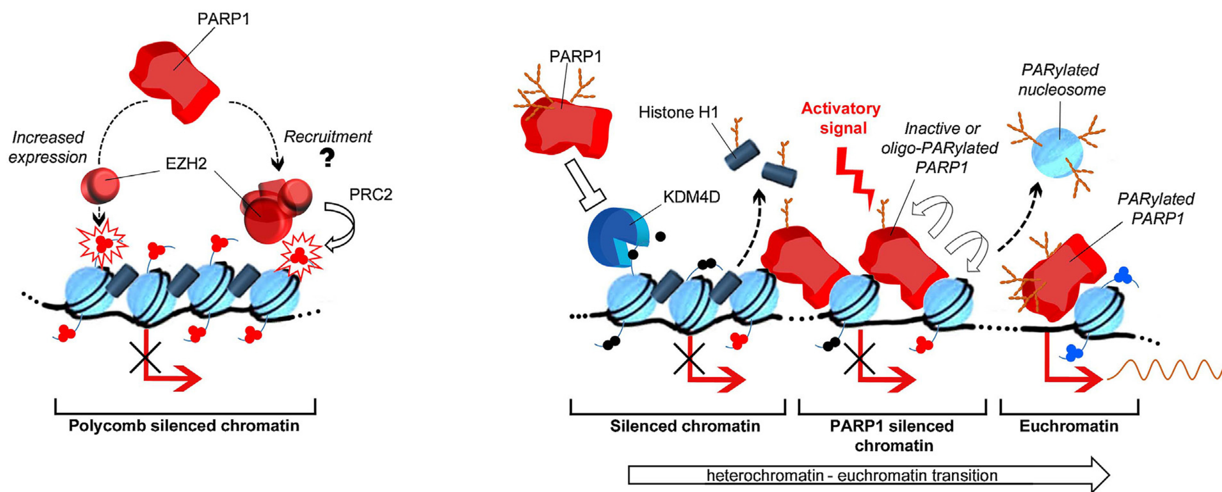

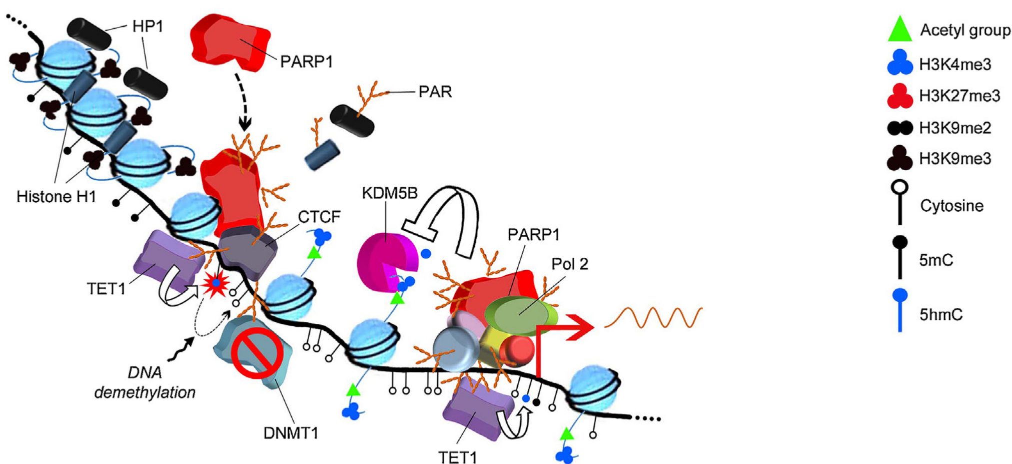

Fig. 2. PARP1 regulates chromatin structure through multiple mechanisms. **(A)** Model of PARP1-activity mediated control of constitutive heterochromatin integrity. PARP1 promotes the interaction of UHRF1 with nucleosomes marked by H3K9me3 and its direct interaction with DNMT1. A PARP1-TIP5-pRNA complex binds specific heterochromatic regions. The pRNA mediates the association between TIP5 and PARP1 and promotes PARP1 activity towards PARP1 itself, TIP5 and histones. PARP1 facilitates the silencing of chromatin also through recruitment of DNMTs. **(B)** Model of the interplay between PARP1 and CTCF in the control of the heterochromatic nuclear lamina associated domains (LADs) involved in the circadian gene expression regulation. Interaction between CTCF and PARP1 mediates the recruitment of specific active chromatin *loci* to the repressive lamina environment, where silencing factors are present. In these conditions the CTCF-PARylated PARP1 resolves, which causes the reactivation of the *locus* **(C)**.

Table 1
General features and putative involvement of PARP1 in the major chromatin domains of genome [80,81].

	Constitutive heterochromatin	Null chromatin	Facultative heterochromatin	Euchromatin
Definition	Highly condensed chromatin whose state is preserved regardless of the cell type. Silencing is based on the HP1 system. Genomic coverage is species-specific and variable (from about 30% to 90%).	Highly repressive chromatin state independent of other silencing systems (PcG and HP1). Lamin proteins at nuclear periphery appear to be the main mediators of silencing and compartmentalization. It covers about 45% of the genome in mammals, depending on cell type.	Chromatin domains that have the capability to convert into euchromatin upon specific signals. Silencing is prevalently based on the action of Polycomb group proteins (PcG) but also on the HP1 system at specific genes.	Fraction of highly accessible and decondensed chromatin showing competence for gene expression.
Chromatin fibre size	≥30 nm fibre.	≥30 nm fibre.	Locally compacted 11 nm fibre.	11 nm fibre.
Genomic constituents	Centromeres, telomeres. Enriched in tandem DNA repeats, transposable elements, satellite DNA and rDNA.	Low gene density. It contains tissue specific and developmentally regulated genes.	Inactive X chromosome, imprinted loci, clusters of silenced genes (*e.g.* HOX genes) and specific silenced gene (mainly CGI-associated genes).	Housekeeping genes and tissue specific genes.
Epigenetic hallmarks	Particularly enriched of: Histone H1, H4K20me3, H3K9me2/me3 and 5mC.	Particularly enriched of: histone H1, H3K9me2/me3 and 5mC (less than 70%).	Particularly enriched of: histone H1 (not necessarily forming the 30 nm fibre but instead involved in forming locally condensed chromatin structures with few nucleosomes), H3K27me3 (+H3K9me2/me3 and 5mC mainly at inactive X chromosome and imprinted loci), H3K27me3 + H3K4me3 at bivalent promoters (mainly CGIs).	Major marks are H3K4me2/3, H3K36me3, H3K9me1, hypoacetylation, DNA hypomethylation and loss of H1.
Chromatin components and trans-acting factors	HP1, Histone deacetylase SIRT1, Histone methyltransferases SUV39H1/2 (H3K9me3) and SUV420H (H4K20me3), UHRF1, MeCP2, DNMT1, 3A and 3B.	Lamin proteins, Emerin, G9a histone methyltransferase (H3K9me2), HDAC1 and 3.	PRC1, PRC2 and other PcGs, MacroH2A (imprinted loci and inactive x chromosome) and HP1 (distinct silenced genes).	ATP-dependent chromatin remodelers, Histone acetyltransferases, Histone methyltransferases (SET1, SET7/9, MLL 1), H3.3 and H2A.Z.
Role of PARP1	Defective PARylation is associated with loss of heterochromatin markers (H3K9me3, H4K20me3 and 5mC) at centromeric heterochromatin. PARylation is required for the maintenance of heterochromatin throughout cell divisions by controlling UHFR1-DNMT1 interplay and DNMT1 expression. PARylation might favour heterochromatin decondensation during DNA damage repair and replication by targeting MeCP2, HP1 and SIRT1.	Active PARylation favours nuclear relocalization of chromatin from centre to periphery by mediating the recruitment of silenced chromatin to the Lamina.	Inactive or minimally modified PARP1 induces the formation of a less condensed inactive chromatin by substituting H1. PARylation controls the CTCF-mediated insulation functions at imprinted loci. PARylation mediates the silencing by H3K9me2 of specific loci by antagonizing the action of the histone demethylase KDM5D. PARylation controls both global and locus-specific accumulation of H3K27me3 by controlling the expression of the H3K27 methylase EZH2.	PARylation of Histones elicits decondensation of chromatin. PARylation favours the accumulation of H3K4me3 at specific loci by antagonizing the histone demethylase KDM5B. PARylation preserves the unmethylated state of CG-rich DNA regions by excluding/inhibiting the DNA methyltransferase DNMT1 and/or by recruiting/activating the 5mC hydroxylase TET1.

Model of PARP1-mediated control of facultative heterochromatin integrity and the heterochromatin-euchromatin transition. PARP1 favours the level of H3K27me3 by the control of *EZH2* expression and by mediating the recruitment of components of the PRC2 to chromatin (left). PARP1 promotes heterochromatin maintenance by contrasting the activity of the H3K9me2 demethylase KDM4D. PARP1 replaces the histone H1 in keeping silent, but less condensed, distinct regions of chromatin. The activation of PARP1 by distinct regulatory signals determines the transcriptional activation of specific genes through a process of chromatin relaxation due to PARylation of chromatin proteins, including histones (right). **(D)** Model of euchromatin control mediated by PARP1activity. PARP1 promotes decondensation of chromatin through PARylation and subsequent removal from chromatin of condensing factors including HP1 and histone H1. The activation of PARP1 could be mediated by transcription factors such as CTCF. PARP1 activation facilitates the demethylation of DNA initiated by the recruitment of TET1 and the subsequent conversion of 5mC into 5hmC but also by the exclusion of DNMT1. Furthermore, PARP1 inhibits the action of the H3K4m3 demethylase KDM5B. PARP1 activity maintains transcription by favouring the positioning and the recycling of Pol2 and transcription factors at active *loci*.
The question marks indicate that the indicated link between events is based on guesses rather than on evidence. Open arrows indicate actions (sharp arrow, positive action; blunt arrow, negative action).

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regulates specific genes conflicting with H3K4me3 demethylation ad H1 loading through the removal of KDM5B functions [35].

Moreover, PARylation delivers KDM5B to DNA damage sites. Local demethylation of H3K4 by KDM5B at DNA lesions contributes to the recruitment of key proteins involved in the DNA-damage response, including Ku70 and BRCA1 [36]. Consequently, PARP1-dependent PARylation of KDM5B might have a double effect on its chromatin association: impairing the binding of KDM5B at active promoters while favouring its accumulation at DNA damage sites.

The action of PARP1 on H3K4me3 extends well beyond the maintenance of steady-state gene expression. In fact, PARP1 mediates the activation of the *PPARγ2* gene during adipocyte differentiation by increasing the H3K4me3 at its promoter in a PAR-dependent manner [37]. The same event associates with the massive induction of *SNAI1* gene upon DNA damage [38]. Notably, an inhibitory function of PARP1 on H3K4me3 has been described for the silencing of *IL-6* gene. In particular, PARP1, independently of its enzymatic activity, impairs trimethylation of H3K4 mediated by the histone methyltransferase MLL at *IL-6* promoter. Following lipopolysaccharides stimulation, PARP1 is dissociated from and MLL binds the *IL-6* promoter leading to increased H3K4me3 and *IL-6* up-regulation [39].

There is also *in vitro* evidence of a direct involvement of PARylation in the crosstalk between H3 and H1 methylation. Accordingly, PARylation of H3 impairs its modification by the H3K4 monomethyltransferase SET7/9, shifting its action towards several lysine residues of H1 [40]. This points to the intriguing possibility of a histone code driven by PARP1 activity but this awaits confirmation *in vivo*.

H3 lysine 9 methylation

H3 lysine 9 methylation (H3K9me) is a hallmark of constitutive and facultative heterochromatin being associated with pericentromeric regions and the inactivated X chromosome along with DNA methylation. From a transcriptional viewpoint, H3K9me2/me3 are enriched at TSS of silenced genes, whereas H3K9me1 is found on the promoters of transcribed genes [41].

Unlike the positive regulation of gene transcription by abrogating KDM5B activity, PARylation can contribute to transcriptional repression by favouring H3K9me2 accumulation at retinoic acid (RA)-dependent genes. In this mechanism, the H3K9me2/me3 demethylase KDM4D is covalently PARylated at the N-term domain. This modification seems to impair KDM4D recruitment onto RA-responsive promoters, which are then inactivated by H3K9me2. Considering that the interaction between the N-term domain and the C-term catalytic domain is necessary for KDM4D demethylase activity, the covalent PARylation of KDM4D N-term domain may also negatively influence the activity of the enzyme. An important role for the activation of RA-target genes is played by the PARG enzyme, which co-localizes with KDM4D at the promoter of these genes restoring the demethylating action following RA stimulation [42].

Furthermore, the interplay between KDM4D and PARylation is key in the DNA-damage response. Here, the covalent PARylation of four residues of the KDM4D C-term domain mediates the recruitment of KDM4D to sites of DNA damage *in vivo* and the subsequent association with chromatin of the DNA-damage response master kinase ATM [43]. Recruitment of KDM4D seems to be also mediated by its non-covalent interaction with PAR [43]. Notably, also the H3K9me2/me3 demethylase [44] and a H3K9 methyltransferase suv39h1-containing complex are recruited to DNA-damage sites in a PARP-dependent manner [45]. However, the function of H3K9me in the regulation of chromatin state around DNA-damage sites is controversial. In fact, although H3K9me3 is necessary for the recruitment of other chromatin enzymes involved in the DNA-damage response, it is detrimental to the recovery of DNA lesions as this typically needs decondensed chromatin to allow the action of the DNA-repair effectors [46].

H3 lysine 27 methylation

H3 lysine 27 trimethylation (H3K27me3) is a typical mark of gene repression. This modification is preferentially introduced at CpG-dense promoters by the lysine methyltransferase EZH2, a component of the Polycomb repressive complex 2 (PRC2). Besides the well-known enrichment of H3K27 trimethylation at inactive promoters, recent high-resolution mapping of histone H3K27 methylations suggests that H3K27me2 impairs the activity of non-cell-type-specific enhancers, whereas H3K27me1 positively transcription [47].

PARylation regulates H3K27me3 by controlling *EZH2* gene transcription. In fact, treatment of lymphoblastic cells with PARP inhibitors causes the up-regulation of *EZH2* gene because of the displacement of the transcriptional repressor E2F4 from its promoter. Increased expression of EZH2 subsequently provokes accumulation of H3K27me3, both globally and at EZH2-target genes [48].

Yeast two-hybrid screening revealed SUZ12, a member of the PRC2 complex necessary for the EZH2-mediated H3K27 trimethylation, among the PARP1 interacting proteins. A functional connection between PARP1/PARylation and SUZ12/H3K27 methylation has been suggested during post-fertilization development for proper localization of SUZ12 onto chromosomes and for the maintenance of H3K27 dimethylation levels in parental pronuclei [49].

Furthermore, PARP1-mediated PARylation is actually necessary for recruitment of the PRC2 complex to sites of DNA damage [50]. The SUZ12/PARP1 interaction could be potentially responsible for this phenomenon. However, the effective enrichment of H3K27 methylation to the DNA-damage response is controversial. On the one hand, a report demonstrated a transient accumulation of H3K27 trimethylation at DNA-damage sites that might be required for recruitment of the downstream repair-associated chromatin modifiers [51]. On the other hand, another report observed the recruitment of EZH2 to DNA damage site with no changes in H3K27 methylation levels [50]. Nevertheless, a general idea is that EZH2 contributes to safeguard genome integrity preventing sensitivity to DNA damage and favouring DNA double strand-break repair [50,51].

2.2. PARP1 in the control of DNA epigenetic modifications

DNA methylation preferentially introduces 5-methylcytosine (5mC) on CpG dinucleotides (CG) by the action of the DNA methyltransferase enzymes (DNMT1, 3A and 3B). 5mC is considered the fifth base of DNA expanding the genetic information into the realm of epigenetics [52]. In mammals, the bulk of DNA is methylated ensuring genome stability in part by suppressing the expression of repetitive elements. The non-methylated residues mainly cluster in discrete regions termed CpG islands (CGIs) accounting for 1% of the genome. CGIs usually overlap the promoter of housekeeping genes (60%) and their non-methylated state guarantees the expression of associated genes. By contrast, methylation of CGIs is associated with long-term silencing [53]. Methylation patterns are created during development and differentiation by the regulated balancing of methylation and demethylation processes [54]. DNA methylation is a combination of maintenance and *de novo* mechanisms. Maintenance methylation occurs soon after replication to transmit methylation patterns to the newly synthetized DNA strand while *de novo* methylation introduces new methyl groups onto DNA [52].

The demethylation process entails the action of the Ten-Eleven Translocation (TET) family of dioxygenases (TET1, TET2 and TET3) which oxidise 5mC to 5-hydroxymethylcytosine (5hmC), now considered to be the sixth base of DNA. TETs contribute

to demethylation by converting 5hmC into 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which are replaced by cytosine through the thymine DNA glycosylase (TDG)-mediated base excision repair (BER). An additional mechanism might involve deamination of 5mC and 5hmC by the AID/APOBEC (Activation-induced deaminase/apolipoprotein B editing complex) enzymes. These mechanisms, allowing the replacement of 5mC with cytosine, represent the active process of demethylation [55]. Passive demethylation occurs by the uncoupling of methyltransferase action/replication, because of multiple mechanisms including DNMT down-regulation and inhibition of DNMT catalysis [52].

Changes in the balancing of PARylation have been identified as one of the mechanisms that can change methylation patterns [11].

PARP1 in the control of DNA methylation

Initial evidence shows that PARP inhibitors increase global 5mC levels, which are associated with chromatin compaction and widespread hypermethylation of CGIs. Later data indicate that PARP1 is a partner of DNMT1 targeted by non-covalent PARylation. Notably, PAR and PARylated PARP1 affect the activity of DNMT1 *in vitro* [11,56]. A model was suggested by which PARylated PARP1 might conflict with CG methylation by non-covalent interaction with DNMT1 preventing its access and action onto DNA [11]. Consistently, PARylation has been reported to preserve the unmethylated state of regulatory sequences of specific genes, including *Dnmt1* [57], *THBD* [58], *α-SMA* [59], *p16* [60], *TET1* [61], the *DMR1* imprinted *locus* [62] and of several pluripotency-related genes [63,64].

PARP1 can also affect DNA methylation by forming a complex with the transcription factor CTCF, a multifunctional chromatin architectural protein involved in maintaining stability of the genomic methylation patterns [62,65,66]. Accordingly, CTCF stimulates PARylation by PARP1, which, in turn, protects CTCF DNA targets sites from methylation through the inactivation of DNMT1 [62,65]. Furthermore, CTCF exists in both covalently and non-covalently PARylated forms. PARylation of CTCF has been proposed to modulate its chromatin regulatory functions and sub-nuclear localization [62,67–70]. In particular, depletion of PAR impedes CTCF from entering the nucleus, which associates with a global increase of epigenetic marks typical of a condensed/inactive chromatin structure, including cytosine methylation [68].

A recent nucleosome-ChIP-seq study has confirmed genome-wide that the enrichment of nucleosome-bound PARP1 predominates in domains showing lower methylation. PARP1 binds within 1-kb from the TSS of highly expressed genes, while it is absent from the promoters of repressed genes. Notably, PARP1-associated nucleosomes overlap CTCF binding sites and DNase I hypersensitive sites showing enrichment in histone marks typical of active chromatin. A parallel genome-wide survey of DNA methylation variation upon PARP inhibition reveals site-specific rather than global changes, with hypermethylation being more frequent than hypomethylation events (72% *vs.* 28%, respectively). In both cases, changes preferentially involve gene-regulatory regions next to TSS, including the CGIs [71].

Indirect links between PARylation and DNA methylation come from the covalent PARylation of UHRF1 and MeCP2. UHRF1 is a DNMT1-interacting protein involved in maintaining heterochromatin CG methylation. PARP1 facilitates the DNMT1-UHRF1 interaction and works counter to the UHRF1-mediated ubiquitination of DNMT1 thereby favouring its stabilization [72]. MeCP2 is capable of binding specifically to methylated DNA and mediates repression of transcription from methylated gene promoters. PARylation of MeCP2 impairs its interaction with chromatin, which suggests that PARP1 is involved in the translation of 5mC signal [73].

PARP1 in the control of DNA demethylation

Earliest observations link PARP1 activation to widespread demethylation of either centromeric or interspersed DNA repeats, possibly because of the inhibition of DNMT1 catalytic activity by PAR [65]. However, the very same effect results by overexpression of the enzyme PARG. In fact, depletion of PAR leads to silencing of *Dnmt1* by hypermethylation, which links demethylation to a defective Dnmt1 maintenance methylation activity [57]. Site-specific demethylation of yet undetermined origins has also been reported for rDNA repeats [74] or gene promoters [71] upon depletion of PARP1 or inhibition of PARylation.

Further clues engage PARylation in the demethylation dynamics. High PARP1 and PAR levels accompany global and site-specific demethylation during early events of the mouse primordial germ cells (PGCs) epigenetic reprogramming towards totipotency [75,76]. The same event concerns the demethylation of the zygotic male pronucleus genome occurring soon after fertilisation of the oocyte [76]. These processes are prevented by the inhibition of PARylation, which is consistent with its auxiliary role in the BER pathway as the final step of the active 5mC removal [75,76]. However, evidence suggests that PARylation also has DNA damage-independent roles in PGCs demethylation, including the ability to induce *Tet1* expression [75]. Subsequent observations highlighted PARP1 as a key positive epigenetic regulator of *TET1* transcription maintaining an active chromatin state of promoter [61,64].

In addition, further roles of PARylation in the control of 5hmC are emerging, which add complexity to the PARylation-TET1 liaison. TET1 is partner of PARP1 and is able to stimulate PARylation by PARP1 *in vitro*, independently of DNA damage [77]. Moreover, TET1 is a target of non-covalent PARylation, which accounts for TET1 recruitment by PPARγ receptor on its target genes, but also for the negative modulation of TET1 hydroxylase activity [77,78]. Further, apart from being target of non-covalent PARylation, TET1 is also covalently PARylated and this has stimulatory outcomes on its activity *in vitro*. However, inhibition of PARylation leads to decreased global levels of 5hmC. This is consistent with the positive role of PARylation in managing TET1 expression and loading onto chromatin. Interestingly, when both these functions are ruled out by the overexpression of an engineered TET1 bringing a specific DNA binding domain, inhibition of PARylation causes an increase of the global level of 5hmC [77]. This suggests that PARylation may even impair TET1 activity *in vivo*. This also fits the finding that PARP inhibitors promote nuclear 5mC-hydroxylase activity [77].

3. PARP1 in the control of the chromatin domains: an integrated view of the epigenetic control of the chromatin architecture by PARylation

Epigenetic processes are a “layer” of gene expression regulation that assists development and differentiation providing stability and mediating adaptive changes of transcriptional programs. Much effort is currently being employed to dissect mechanisms underlying epigenetic events especially where defective epigenetic regulation results in disease, such as cancer, metabolic and neurodegenerative diseases. However, driving mechanisms that control epigenetic patterns still remain elusive because epigenetic regulation has a mutual relationship with even more complex regulatory processes involved in the three dimensional structure of chromatin [79]. The recent investigation of global chromatin landscapes revealed that the vast majority of the genome is covered by discrete chromatin domains falling into four categories: constitutive and facultative heterochromatin, null chromatin and euchromatin. Each shows rather distinct constituents, epigenetic markers, 3-D structures and spatial arrangement within the nucleus (Table 1) [80,81].

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Evidence indicates PARP1 as new incomer in the complex framework of chromatin regulation having an impressive array of different roles. PARP1 can replace, displace, recruit and modulate the activity of multiple structural and regulatory chromatin factors in order to mould chromatin with implications for transcription and DNA repair. With its functional multiplicity, PARP1 stands out against the other chromatin modifiers.

Compelling evidence suggests that PARP1 has a role in the maintenance and dynamic regulation of the different chromatin domains (Table 1, Fig. 2).

Concerning constitutive heterochromatin, PARylation is required to preserve its integrity. PARP1 and other PARP family members are fundamental constituents of the different heterochromatic chromosomal/nuclear compartments (*e.g.* centromeres, telomeres, nucleolar heterochromatin) [82]. The deficiency of PARPs is associated with heterochromatin-related phenotypes, including telomere dysfunction, disorganization of centromeric heterochromatin with concomitant chromosome miss-segregation [82]. Consistently, inhibition/depletion of PARPs causes loss of fundamental heterochromatic epigenetic markers such as H3K9me3 [74], H4K20me3 [72], and 5mC [57] at centromeric regions. Particularly, PARylation conflicts with the histone demethylases KDM4B/D that might be required to preserve H3K9me3 [42–44]. PARP1 and UHRF1 cooperate in the accumulation of H4K20me3 and in the stabilization of DNMT1. Moreover, PARP1 favours the interaction of UHRF1 with DNMT1, which is necessary to direct DNMT1 to H3K9me3-rich chromatin and hemi-methylated CG dyads [72]. This, together with the positive transcriptional control on *DNMT1* [57], suggests that PARP1 is involved in maintaining heterochromatin epigenetics throughout DNA replication. Consistently, PARP1 favours the re-establishment of rDNA and pericentric heterochromatin through the loading of repressive factors (*e.g.* NoRC [74]) (Fig. 2A).

In the context of DNA replication and, even more, during DNA damage repair, PARP1 activity may favour heterochromatin decondensation by restricting the functions of HP1 [83], MeCP2 [73] and of the histone deacetylase SIRT1 [32].

PARP1 participates in the reversible compartmentalization of chromatin in the repressive lamina-associated domains (LADs) of the null chromatin, as described for the circadian regulation of gene expression. In this context, PARP1 is catalytically activated by CTCF and changes the CTCF-mediated inter-chromosomal network permitting the recruitment to the lamina and the H3K9me2-mediated silencing of specific active *loci*. CTCF-PARP1 interaction exhibits a circadian rhythm so that, once this complex degrades, the silenced *locus* is released from the lamina and regains transcriptional activity [84]. Consistently, PARylation facilitates the association of multiple insulator proteins with the nuclear lamina in *Drosophila*, which indicates a key role of PARP in the formation of null chromatin domains [85]. Whether the previously described PARylation of Lamin proteins and their interaction with PARP1 [86] participate in these processes remain to be seen (Fig. 2B).

PARP1 also controls conditionally repressed genes (*e.g. Hsp70*) [17,87], imprinted genes [70] and the inactive X-chromosome [18] as part of the facultative heterochromatin. In this context, by performing histone H1-like functions, inactive or oligo-PARylated PARP1 associates with less condensed chromatin that needs to be decondensed following PARP1 activation [24]. Further, PARylation controls the CTCF-mediated insulation functions at imprinted *loci* [70] and the genomic distribution and levels of the two major facultative heterochromatin histone epigenetic modifications H3K9me2 [42] and H3K27me3 [48] (Fig. 2C).

An unexplored, but feasible, action of PARP1 could be envisaged in the maintenance of bivalent promoter epigenetics by coupling maintenance of H3K4me3 [35], DNA hypomethylation [11], TET1 occupancy/activity [77,78] and possibly the recruitment of PRC2 complex [49]. This could contribute to the capability of PARP1 to control pluripotency, which requires the poised state of bivalent promoters at differentiation-associated *loci* [63,64].

By the same mechanisms, PARP1 may grant chromatin plasticity and ultimately elicit heterochromatin to euchromatin transition, which implies the existence of *locus*-specific control of PARP1 activity. Converging evidence indicates that DNA structures and several proteins may regulate and provide docking sites for PARP1 at promoters and distal *cis*-regulatory sequences. Major examples include histone variants [16,18–20], nuclear receptors [26,78], transcription factors (TFs) and unmethylated-CG binders (*e.g.* HSF [17], CTCF [62,65,70] and TET1 [77]) (See the Graphical Abstract). PARP1 has also been described as resident chromatin epigenetic factor "bookmarking" promoters in mitotic chromosomes that have to be de-compacted and reactivated in newly formed daughter cells after cell division. This suggests PARP1 acting as a genome-wide memory marker required for cells to maintain their epigenetic identities throughout generations [88].

The mechanisms used by PARP1 to induce euchromatin formation go well beyond its well-known capability of disrupting chromatin structure by histones PARylation to give access to the transcriptional apparatus. In fact, the PARP1 position in the genome shows anti-correlation with DNA methylation and maps to transcriptionally active chromatin regions characterized by typical euchromatic markers such as H3K4me3 and H3K36me3 [71]. The underlying mechanism could be that PARylation by PARP1 forms a local chromatin environment able to exclude repressive epigenetic modifiers (*e.g.* the DNA methylase DNMT1 [56,62,65], the H3K4 demethylase KDM5B [35]) and to recruit activators (*e.g.* the 5mC-hydroxylase TET1 [77,78], and the acetyltransferase CBP [20,30]). Consistently, PAR accumulates at active gene *loci* where they assemble a supra-molecular structure that elicits and maintains an active chromatin configuration and aids transcription by locally retaining TFs and Pol2 [87] (Fig. 2D). Notably, many epigenetic mechanisms controlled by PARP1 at euchromatic *loci* are known to be interdependent like the unmethylated state of CGIs and their occupancy by TFs, TET1, Pol2 and H3K4me3 [52], thus suggesting PARP1 as an underlying common regulator. Taken together, this paints a rather complex picture, depicting PARP1 standing at the crossroads of histones and DNA epigenetic modifications that define euchromatin epigenetics. Particularly, H3K4me3 is thought to be established genome-wide by the CFP1 protein, which recognizes unmethylated DNA *via* its unmethylated-CG binding domain (CxxC) and recruits the H3K4 histone methyltransferase SET1 [89]. The preservation of H3K4me3 by counteracting the KDM5B activity [35], the inhibition/exclusion of DNMT1 [56,62,65], the recruiting/modulation of TET1 [77] for the removal of spurious 5mC and the retention of Pol2 and TFs [90] may be cooperative mechanisms that PARP-1 can orchestrate to maintain the unmethylated state of CGIs. In this process, PARP1 might be helped by chromatin factors that preferentially bind unmethylated CG such as CTCF, which has been described as being capable of recruiting and activating PARP1 at specific CG-rich *loci* thereby protecting their unmethylated state [62,65].

4. Conclusions

Accumulating evidence suggests extensive cross-talk between different epigenetic pathways and PARylation. Much of the available data relates to PARP1. However, the involvement of other members of the PARP family cannot be excluded. In fact, while the Parp1 knock-out mice develop normally [91] despite the multiple functions of PARP1 in epigenetics, Parp1/Parp2 double-knockout mice die in early embryogenesis [92]. Moreover, a role of other PARPs (*i.e.* PARP3 [93] and PARP7 [64]) in the control of epigenetic

processes has been proposed. This suggests a potential functional redundancy of some PARPs in the epigenetic regulation of chromatin structure.

PARP1 has been broadly associated with active chromatin. However, in a seemingly opposing function, PARP1 is also important for ensuring the integrity of constitutive and facultative heterochromatin. By overlaying these diverse effects on chromatin configuration, this review builds an integrated perspective where PARP1 controls global chromatin homeostasis by orchestrating multiple epigenetic mechanisms. This sets a "knowledge framework" that may form an understanding for the mechanisms underlying the dynamic changes of the epigenome that drives both physiological processes such as development, differentiation and a growing number of diseases.

Significantly, these actually are the research areas where the dominant role of PARylation in epigenetics is becoming increasingly evident, as in the case of the epigenetic control of cancer-related genes [60] and the global resetting of the epigenome that accompanies early embryogenesis [75,76] and the differentiation of stem-cells [63,64].

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