The International Journal of Biochemistry & Cell Biology 41 (2009) 60–65

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Review

The role of poly(ADP-ribosyl)ation in epigenetic events

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ARTICLE INFO

Article history:
Available online 14 August 2008

Keywords:
Poly(ADP-ribosyl)ation
Epigenetics
Chromatin structure and function

ABSTRACT

Epigenetic refers to a range of heritable chromatin modifications including DNA methylation, histone modifications, remodeling of nucleosomes and higher order chromatin modifications. In the framework of chromatin remodeling activities, the poly(ADP-ribosyl)ation of nuclear proteins catalyzed by PARPs, particularly PARP-1 and PARP-2, plays a fundamental role and as such have the potential to orchestrate various chromatin-based biological tasks including transcription, DNA repair and differentiation. In this review, we propose a short overview of the more recent experimental data that shed light on the role of poly(ADP-ribosyl)ation in the translation of the histone code. We will essentially focus on the different mechanisms by which PARP activity regulates the global chromatin environment and how this affects cellular pathways.

Contents

1. Introduction

Poly(ADP-ribosyl)ation is a post-translational modification of proteins mediated by poly(ADP-ribose) polymerases (PARPs). Using NAD^+ as a substrate, PARPs catalyze the covalent attachment of ADP-ribose units on the glutamic or aspartic acid residues of target proteins, to generate long linear and branched poly(ADP-ribose)(PAR) chains. This reaction is reversible owing to the endo- and exo-glycosidic activity of poly(ADP-ribose)glycohydrolase (PARG).

PARP-1, the founding member of the PARP family (17 members) and PARP-2, have long been studied as DNA damage responsive enzymes required for the maintenance of genome integrity. They are both activated by DNA strand interruptions, heterodimerize, share several common nuclear binding partners and have been described as active players of the single-strand break repair/base excision repair process (SSBR/BER) (Dantzer et al., 2000; Schreiber et al., 2002, 2006). Recent insights into the involvement of PARP-1 and PARP-2 in transcriptional regulation under physiological conditions (reviewed in Kraus, 2008) and their particular role in

Abbreviations: PARP, poly(ADP-ribose) polymerase; PAR, poly(ADP-ribose); SSBR/BER, single-strand break repair/base excision repair; PARG, poly(ADP-ribose) glycohydrolase.

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doi:10.1016/j.biocel.2008.07.023

the maintenance of constitutive and facultative heterochromatin integrity (Dantzer et al., 2004; Meder et al., 2005; Saxena et al., 2002a,b; Schreiber et al., 2006; Yelamos et al., 2008) aid to the emerging view that poly(ADP-ribosyl)ation might play a key role in the epigenetic regulation of chromatin dynamics. In this paper, we concentrate on recent literature to encompass the different mechanisms by which PARP activity regulates the global chromatin environment.

2. The impact of poly(ADP-ribosyl)ation on global chromatin environment

2.1. Poly(ADP-ribosyl)ation modulates the structure and composition of chromatin

The poly(ADP-ribosyl)ation of polynucleosomes and the associated relaxation of chromatin structure were the initial demonstration of a role of PAR in the regulation of chromatin dynamics (Huletsky et al., 1989; Poirier et al., 1982; Rouleau et al., 2004). Biochemical and *in vivo* studies in humans and *Drosophila* have since complemented this observation and further showed that PARP-1 contributes to either the compaction or decondensation of the chromatin depending on the physiological conditions. In *Drosophila*, PARP-1 was shown to be essential for the formation and organization of heterochromatic structure (Tulin et al., 2002). However when activated in response to immune challenge, stress and steroid hormones, PARP-1 induces a dramatic loosening of local chromatin structure that promotes transcription of highly inducible genes (Tulin and Spradling, 2003).

Although the mechanism involved remains unknown, recent advances in mammalian cells extend this observation to a role of PARP-1 in modulating the composition of chromatin. Compelling recent studies define PARP-1 as a regulated promoter-specific exchange factor required for the activation of specific gene programs. Indeed, the catalytic function of PARP-1 was shown to facilitate (i) the release of histone H1 from a subset of PARP-1-targeted PolII-transcribed promoters (Krishnakumar et al., 2008), (ii) the consequent recruitment of the chromatin architectural protein HMGB1 on the estrogen-stimulated pS2 promoter (Krishnakumar et al., 2008), (iii) the dissociation of the repressor DEK from chromatin that permits the loading of the RNA PolII mediator complex (Gamble and Fisher, 2007), (iv) the dismissal of the TLE1 corepressor complex from the MASH1 promoter during neural stem cell differentiation that also results in the phosphorylation and activation of the HES transcription factor (Ju et al., 2004) and (v) the heat shock-induced ADP-ribosylation and displacement of the *Hsp70.1* promoter-associated macroH2A1.1 and the core histones H3 and H2B (Ouararhni et al., 2006).

Importantly, PARP-1 is also likely to control some aspects of chromatin structure independently of its enzymatic activity. In *Drosophila*, the expression of an enzymatically inactive PARP-e isoform during oogenesis and early larval development controls the transcription of the heterochromatic gene *PARP-1* either by acting on the promoter or by facilitating heterochromatin formation (Tulin et al., 2002). In addition, recent biochemical assays combined with atomic force microscopy with reconstituted chromatin have revealed a functional cooperation between the catalytic and the DNA-binding domain of PARP-1 that promotes chromatin compaction and transcriptional repression in a manner independent of poly(ADP-ribose) synthesis (Kim et al., 2004; Wacker et al., 2007).

2.2. Poly(ADP-ribosyl)ation modulates chromatin dynamics

Many initial *in vitro* studies suggest that PARP-1 associates to chromatin by binding to histones, preferentially histones H2A and H2B (Buki et al., 1995). By contrast, *Drosophila* histone H1 was reported as an antagonist of PARP-1 binding to chromatin (Kim et al., 2004). FRAP assays performed in *Drosophila* revealed a continuous exchange between the soluble and the chromatin-associated PARP-1 as well as between chromatin domains independently of its catalytic activity (Pinnola et al., 2007). More specifically, PARP-1 interacts with the core histones H3 and H4 in the context of nucleosome. Whereas the N-terminal tail of histone H4 works as an activator of PARP-1, histone H2A inhibits the protein. The authors propose a model in which developmental and/or environmental stimuli induce local changes in the histone modification code and subsequently expose and/or hide specific histone domains which activate and/or inhibit PARP-1.

More recently, we also identified the heterochromatin proteins HP1α and HP1β as efficient targets for PARP-1 and/or PARP-2 binding *in vitro*. Both PARPs selectively poly(ADP-ribosyl)ate HP1α. These data describe PARP-1 and PARP-2 as new actors of the HP1-mediated subcode histone underlying the histone code, and opens the way to forthcoming fascinating issues aimed to understand the contribution of poly(ADP-ribose) in HP1-mediated pericentric heterochromatin structure and function (Quénet et al., 2008).

2.3. Regulation of PARP activity within chromatin

The poly(ADP-ribose)-dependent modulation of chromatin structure and activity is a dynamic process that requires additional cellular pathways. One challenge to face includes the ready (and probably localized) supply of NAD^+. Recent *in vitro* biochemical studies have clearly shown that the availability of NAD^+ regulates the effect of PARP-1 on chromatin structure and transcription. In the absence of NAD^+, saturating binding of PARP-1 to nucleosomes promotes chromatin compaction and inhibition of transcription, whereas high amount of NAD^+ induces PARP-1 automodification, its release from nucleosomes, chromatin relaxation and transcription (Kim et al., 2004; Wacker et al., 2007). How a regulated supply of NAD^+ occurs at chromatin regions *in vivo* remains unknown. One can envisage a tight regulation of the enzymatic activities involved in NAD^+ biosynthesis such as the NAD^+ synthase NMNAT-1 by either post-translational modifications or recruitment to chromatin sites where PARPs act. In this regard, NMNAT was shown to regulate PARP-1 activity depending on its state of phosphorylation (Berger et al., 2007). In addition, the functional interplay between PARPs and other chromatin-associated NAD^+-consuming enzymes such as the histone deacetylase SirT1 also provides an interesting way to regulate NAD^+ availability at specific sites (Kolthur-Seetharam et al., 2006). In line with this idea, excessive ADP-ribosyl)ation of SirT1 in the absence of PARG in *Drosophila* drives SirT1 delocalization from the nucleus and inhibits its chromatin silencing activity of the copia retrotransposon (Tulin et al., 2006). This observation underlines the catabolism of poly(ADP-ribose) by PARG as an additional level of regulation within chromatin.

Equally important may be the physiological inducers of PARP activity at chromatin. Whereas the efficient activation of PARP-1 upon genotoxic insult is highly documented, still limited information is available for its activation in a physiological context. One strategy relates to the generation of tightly controlled physiological DNA strand breaks and repair. For example, the estrogen-induced demethylation of the bcl-2 promoter produces high burst of DNA oxidation that in turn recruits the base excision repair proteins OGG1 and DNA topoisomerase-IIβ (Perillo et al., 2008). This process triggers chromatin conformational changes that are essential for estrogen-induced transcription. Similarly, the expression of the estrogen-regulated *TFF1* gene is associated with the recruitment of the DNA-repair enzymes PARP-1, DNA-PK and DNA topo IIβ to the