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Transcriptional Control by PARP-1: Chromatin Modulation, Enhancer-binding, Coregulation, and Insulation

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Summary

The regulation of gene expression requires a wide array of protein factors that can modulate chromatin structure, act at enhancers, function as transcriptional coregulators, or regulate insulator function. Poly(ADP-ribose) polymerase-1 (PARP-1), an abundant and ubiquitous nuclear enzyme that catalyzes the NAD^+-dependent addition of ADP-ribose polymers on a variety of nuclear proteins, has been implicated in all of these functions. Recent biochemical, genomic, proteomic, and cell-based studies have highlighted the role of PARP-1 in each of these processes and provided new insights about the molecular mechanisms governing PARP-1-dependent regulation of gene expression. In addition, these studies have demonstrated how PARP-1 functions as an integral part of cellular signaling pathways that culminate in gene regulatory outcomes.

Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1) is an abundant (as many as 1 to 2 million copies per cell [1]) and ubiquitous nuclear enzyme with biochemical properties that make it ideally suited for the regulation of nuclear processes. Although originally characterized as a key factor in DNA repair pathways, a wealth of studies over the past decade have demonstrated a role for PARP-1 in the regulation of gene expression under basal, signal-activated, and stress-activated conditions [1–3]. Recent studies using a variety of experimental approaches have highlighted the role of PARP-1 in at least four distinct modes of transcriptional regulation (see below) and provided new insights about the cellular signaling systems that interface with PARP-1 in the nucleus.

PARP-1, the founding member of the PARP superfamily [4], has a carboxyl-terminal catalytic domain that polymerizes linear or branched chains of ADP-ribose (ADPR) from donor nicotinamide adenine dinucleotide (NAD^+) molecules on target proteins (Fig. 1) [1,2]. Poly (ADP-ribosyl)ation (PARylation) by PARP-1 is likely the major source of poly(ADP-ribose) (PAR) production in the cell [1]. PARP-1 also has an amino-terminal DNA binding domain (DBD) containing two zinc finger motifs, as well as a central automodification domain (AMD) that functions as the target of direct covalent automodification [1,4] (Fig. 1a). Together, these domains allow PARP-1 to interact with genomic DNA and chromatin, poly(ADP-ribosyl)ate relevant nuclear targets, and regulate gene expression. Studies from the past few years, which will be the focus of this review, have begun to elucidate the underlying mechanisms and consequences of gene regulation by PARP-1.

PARP-1 activities and interactions

The biochemical activities of PARP-1 provide clues to how it might function in gene regulation in vivo. High affinity binding of PARP-1 to certain forms of DNA (double strand breaks, cruciforms, crossovers) and nucleosomes are mediated by the DBD [1,3,5–8]. PARP-1's enzymatic activity is low in basal or unstimulated conditions, but is potently allosterically activated by the binding of PARP-1 to a variety of interaction partners, including protein interaction partners, nucleosomes, and the aforementioned forms of DNA [1,3,5,7,9]. A newly identified third zinc binding domain located between the second zinc finger and the AMD (Fig. 1a) couples DNA binding to the allosteric activation of PARP-1's catalytic activity [10•]. Numerous nuclear targets for PARP-1 enzymatic activity have been identified, including core histones, the linker histone H1, and a variety of transcription factors, but PARP-1 is the major acceptor for PARP-1-dependent poly(ADP-ribosyl)ation (PARylation) reactions in vivo [1, 3].Automodification blocks the ability of PARP-1 to bind to both DNA and nucleosomes [1, 5,6•].

In addition to its interactions with DNA and substrates, PARP-1 associates with complexes containing a variety of other nuclear proteins, including transcription-related factors [11]. Recent studies have demonstrated functional associations of PARP-1 with a variety of regulatory complexes, including a TLE (Transducin-like enhancer of Split) corepressor complex [12], a Mediator coregulator complex [13], a condensin I/XRCC1 repair complex [14], a macroH2A1.1 nucleosome complex [15••], and a CTCF insulator complex [16,17]. As highlighted below, interactions with these protein partners dictate the location and actions of PARP-1 in gene regulation.

PARP-1 genomics

Understanding the role of PARP-1 in gene regulation requires knowledge of where PARP-1 binds in the genome and which genes are directly regulated by its actions. Recent genomic studies have begun to provide answers to these questions. Chromatin immunoprecipitation coupled to hybridization to genomic microarrays (i.e., ChIP-chip) has shown that PARP-1 binding is enriched at the promoters of perhaps as many as 90 percent of expressed RNA polymerase II (Pol II)-transcribed promoters in MCF-7 cells [18••]. Interestingly, the enrichment of PARP-1 at these promoters correlates with the depletion of the linker histone H1, and a high PARP-1/H1 ratio specifies genes that are actively transcribed. This does not, however, imply a stimulatory role for PARP-1 at all of these promoters, but rather indicates that PARP-1 localizes to sites of ongoing transcription, where it may in fact exert stimulatory or inhibitory effects [18••]. Although PARP-1 localizes to actively transcribed promoters, its localization pattern may not completely overlap that of active (i.e., phosphorylated) Pol II in a given gene [5] since PARP-1 generally peaks just upstream of the transcription start site (i.e., approximately −250 bp), whereas active Pol II localizes to the transcription start site and the body of the gene [18••].

Microarray expression analyses using cells and tissues derived from PARP-1-deficient (*Parp-1*$^{-/-}$) mice have begun to yield information about the PARP-1-regulated transcriptome [19–21]. In a recent study exploring gene expression profiles in embryonic stem cells and livers from *Parp-1*$^{-/-}$ mice, ~3.5% of the transcriptome was regulated by PARP-1, with approximately 60 to 70% of the genes being positively regulated by PARP-1 [19]. The regulated gene sets play roles in critical cellular processes such as metabolism, stress responses, signal transduction, cell cycle control, and transcription, fitting well with the known functions of PARP-1 [19], but perhaps a bit surprising given the mild overall phenotype of *Parp-1*$^{-/-}$ mice [22].

The difference between the large number of PARP-1-bound promoters from ChIP-chip analyses and the limited number of PARP-1-regulated genes from expression analyses is striking, but perhaps not unexpected. A number of genomic analyses have revealed more genomic binding sites than regulated genes for a variety of factors. In the case of PARP-1, this may suggest that other factors, including related nuclear PARPs (e.g., PARP-2) [4], play redundant regulatory roles at many PARP-1-bound promoters and mask the effects of PARP-1 depletion or inhibition [2]. Alternatively, PARP-1-dependent regulation of some PARP-1-bound promoters may only occur in certain cell types or in response to appropriate cellular signals. In contrast, the localization of PARP-1 to some actively transcribed promoters may occur as a consequence of the transcription process (e.g., histone modification; cleavage or oxidation of promoter DNA [23••,24]) without PARP-1 playing a specific role in the regulation of those promoters. In this regard, PARP-1 may have an alternate role in promoter-localized transcription-coupled DNA repair distinct from the regulation of transcription initiation [14, 23••–25], although such speculation requires additional proof.

Modulation of chromatin structure and composition by PARP-1

The earliest characterized effects of PARP-1 on the genome were the modulation of chromatin structure and the PARylation of histones [1,3,26,27] (Fig. 2a). The effects of PARP-1 on chromatin structure have been elaborated and elucidated in more recent biochemical and in vivo studies [5,6•,28,29.]. For example, biochemical assays have shown that PARP-1 binds to nucleosomes at the dyad axis with a stoichiometry of one [5]. Saturated PARP-1 binding to nucleosomes in the absence of NAD^+ promotes the compaction of nucleosomal arrays into higher order structures [5], as recently visualized by atomic force microscopy [6•] (Fig. 3a). These PARP-1-dependent higher order structures are refractory to in vitro transcription [5, 6•]. In the presence of saturating amounts of NAD^+, PARP-1 automodifies and releases from the chromatin, leading to decompaction and the restoration of transcription [5,6•] (Fig. 3c). At first glance, these results may seem at odds with the genomic studies described above [18••]. How is PARP-1 binding at promoters associated with actively transcribed genes in vivo when it promotes chromatin compaction and transcriptional repression in vitro? The reason may be the NAD^+ concentrations, with the former occurring at a physiological nuclear NAD^+ concentration and the latter occurring in the non-physiological absence of NAD^+ [5,6•,18••] (Fig. 3). Thus, although PARP-1 can bind to nucleosomes and promote saturating levels of chromatin compaction in vitro, more studies are needed to determine the extent to which PARP-1 compacts chromatin at promoters in vivo.

Recent studies have suggested a role for PARP-1 in regulating the composition of chromatin (Fig. 2a). For example, PARP-1 acts to exclude H1 from the promoters of some PARP-1-regulated genes [18••], possibly by competing with H1 for binding to nucleosomes [5] or by PARylating it [27]. Furthermore, during estrogen-induced transcription of the *TFF1* (a.k.a. *pS2*) gene, PARP-1 not only promotes the removal of H1, but also increases the levels of HMGB1, a chromatin architectural protein that enhances transcription [23••]. In addition, PARP-1-dependent PARylation of DEK, an abundant and ubiquitous component of chromatin, promotes the release of DEK from chromatin, the loading of the Mediator coregulatory complex, and the enhancement of transcription [30•]. PARP-1-dependent PARylation may also affect the genomic actions of SIRT1, an NAD^+-dependent histone deacetylase [2].

Two recent studies have suggested that interactions between PARP-1 and the histone variant macroH2A, an H2A variant containing a large carboxyl-terminal non-histone region called a "macro" domain, may provide another means for bringing PARP-1 to chromatin and regulating PARP-1 enzymatic activity [15••,31•]. The common observations from these studies are: (1) binding of PARP-1 to the "non-histone" domain of macroH2A1 (splice variants 1.1 or 1.2) and (2) inhibition of PARP-1 enzymatic activity by macroH2A (full length 1.1 [15••] or the non-

histone domain from 1.1, 1.2, or 2 [31•]). In spite of these similarities, RNAi-mediated depletion of macroH2A1 or PARP-1 differentially affects the expression of target genes in the two systems studied. Specifically, depletion of macroH2A1 or PARP-1 blocks heat shock-induced expression of the *HSP70.1* gene in HeLa cells [15••], but reactivates expression of an inactive X (Xi)-linked GFP transgene in mouse embryo fibroblast cells [31•]. Further studies are required to fully understand the functional link between PARP-1 and macroH2A.

Enhancer-binding actions of PARP-1

Many of the initial studies describing direct effects of PARP-1 on the transcriptional regulation of target genes focused on the binding of PARP-1 to specific DNA sequences or structures in the regulatory regions of the genes, allowing PARP-1 to function like a classical enhancer-binding factor [32–36] (Fig. 2b). In fact, direct binding of PARP-1 to hairpins may underlie an autoregulatory mechanism governing the expression of the *PARP-1* gene itself [37]. Two recent studies have examined the role of direct DNA binding by PARP-1 in the regulation of the PARP-1 target genes *CXCL1* [38•] and *BCL6* [39•]. PARP-1 binds to specific sequences immediately upstream of the *CXCL1* promoter and in the first intron of *BCL6* to repress transcription. For *CXCL1*, the binding of PARP-1 inhibits expression by preventing the binding of NF-κB to an adjacent element, an effect that is reversed upon PARP-1 activation and automodification, resulting in a loss of PARP-1 binding to the promoter [38•]. The generality of enhancer-binding as a mode of transcriptional regulation is unknown. As the determinants of PARP-1 binding to DNA are elucidated, bioinformatic analyses may aid in the identification of new PARP-1 target genes subject to this type of control.

Transcriptional coregulation by PARP-1

Roles for PARP-1 as a promoter-specific coregulator (either a coactivator or a corepressor) for a number of different sequence-specific DNA-binding transcriptional regulators, such as NF-κB, nuclear receptors, HES1, B-Myb, Oct-1, HTLV Tax-1, Sp1, NFAT, Elk1, and others, have been reported [2,3,12,13,40–43••] (Fig. 2c). In most of these cases, the DNA-binding factor is thought to recruit PARP-1 to relevant target promoters. Yet, ChIP-chip analyses have shown that many peaks of promoter-proximal PARP-1 binding are quite broad (i.e., as much as 3 kb or more shoulder to shoulder) [18••]. How such a genomic localization pattern relates to recruitment by a DNA-binding factor to a specific site is not clear. In some cases, PARP-1 enzymatic activity is not required for its coregulatory activity (e.g., with NF-κB, B-Myb, and HTLV Tax-1) [2,3,40], while in others it is required (e.g., HES1, Sp1, NFAT, and Elk1) [12, 41–43••]. In many of the latter cases, the DNA-binding factor or other components of the coregulatory complex are targets for PARP-1-dependent PARylation [12,41,42].

A key question regarding PARP-1 coregulatory activity is the effect that it has on the transcription complexes assembled at target promoters. Recent studies have shown that PARP-1 can function as a promoter-specific "exchange factor" that promotes the release of inhibitory factors and the recruitment of stimulatory factors during signal-regulated transcriptional responses [12,13,23••]. For example, PARP-1 has been shown to promote the exchange of a TLE1 corepressor complex for a HAT-containing coactivator complex with HES1 during signal-dependent activation in neuronal cells [12]. Likewise, PARP-1 can promote the exchange of an inactive cdk8-positive Mediator for an active cdk8-negative Mediator during retinoic acid-regulated activation [13].

More recently, a study describing perhaps the most intriguing actions of PARP-1 at promoters has added a new twist to the exchange factor model [23••]. In this study, PARP-1 was shown to promote the recruitment of topoisomerase IIβ (TopoIIβ) to hormone-regulated promoters, leading to concomitant promoter DNA cleavage, factor exchange, and transcriptional activation [23••,44,45]. The study focused on the estrogen-regulated *TFF1* gene promoter,

which is bound by a PARP-1 corepressor complex containing the corepressor NCoR and the histone deacetylase HDAC3 prior to activation. Estrogen exposure rapidly promotes an exchange of the corepressor complex for a PARP-1 coactivator complex containing TopoIIβ, the coregulator ASC2, and the DNA repair proteins Ku86/70 and DNA-PK. This results in a transient TopoIIβ-dependent cleavage of the promoter DNA near the estrogen receptor binding site, which may resolve a topological barrier and allow for favorable structural changes at the promoter. Recruitment of the PARP-1 coactivator complex also promotes the release of histone H1, the recruitment of HMGB1/2, changes in chromatin architecture, and ultimately increased transcription of the gene [23••,44,45]. Together, these studies highlight the diverse mechanisms of PARP-1 coregulator function, which are likely to vary in an activator-and gene-specific manner.

Insulator functions of PARP-1: CTCF, the nuclear matrix, and DNA methylation

Insulators are DNA elements that help to organize the genome into discrete regulatory units by limiting the effects of enhancers on promoters or by preventing the spread of heterochromatin [46]. Recent studies have implicated PARP-1-dependent PARylation of CTCF, a ubiquitous DNA-binding protein that functions at insulators, in the preservation of insulator function [16,17,47] (Fig. 2d). In this regard, the general PARP inhibitor 3-aminobenzamide blocks insulator function in cell-based assays [16,17,47]. PARP-1 actions at insulators may also involve associations with the nuclear matrix and DNA methylation, both of which have been implicated in insulator function [46,47]. Note, for example, that CTCF, PARP-1, and PARP-1-associated proteins (e.g., nucleophosmin, topoisomerase II, Ku, DNA-PK) have been shown to associate with components of the nuclear matrix [17,48–51]. In addition, PARP-1 has been shown to regulate DNA methylation [52,53], perhaps through the regulation of the DNA methyltransferase DNMT1 [54], and DNA methylation can modulate the binding of CTCF to insulators [55]. Additional studies are needed to clarify the role of PARP-1 in insulator function, especially as it relates to the regulation of PARP-1 target genes.

Signaling and regulation in PARP-1-dependent gene expression pathways

A number of cellular signaling pathways culminate with the regulation of PARP-1-dependent transcriptional processes (Fig. 4). Mediating signals include small molecules (e.g., steroid and vitamin hormones) [13,23••], heat shock [15••,29], and kinases (e.g., CaM kinase IIδ and ERK2) [12,43••]. Cellular signaling may result in the post-translational modification of PARP-1 through autoPARylation [43••], acetylation [56], or phosphorylation [57•,58], which alter PARP-1 activity for gene-specific or other regulatory outcomes.

A recent study has revealed an interesting alternate signal-dependent mechanism for the activation of PARP-1 enzymatic activity that does not require DNA binding by PARP-1 [43••]. The binding of PARP-1 by ERK2 potently stimulates PARP-1 enzymatic activity and, as a result, increases PARP-1 autoPARylation. Upon activation, PARP-1 promotes the ERK2-dependent phosphorylation of a downstream effector, the DNA-binding transcription factor Elk1, resulting in an increase in histone acetylation and target gene expression [43••]. Direct phosphorylation of PARP-1 by ERK1/2 may also enhance PARP-1 activity, but the effects on transcription have not been determined [57•]. Another recent study has suggested a means by which promoter-localized effects of signaling might promote DNA oxidation-dependent PARP-1 actions at promoters [24]. Estrogen-induced demethylation of histones by LSD1 at the *BCL-2* gene generates H_2O_2 that can oxidize the promoter DNA, leading to the recruitment of components of the base excision repair machinery (e.g., OGG1) and TopoIIβ [24], which could conceivably recruit and activate PARP-1 (Fig. 4). The latter is reminiscent of the

estrogen-induced recruitment of TopoIIβ to the *TFF1* gene promoter [23••]. Whether such a mechanism also involves the recruitment of PARP-1, however, has not been determined.

The regulation of nuclear NAD^+ synthesis and PAR catabolism represent additional points of control for PARP-1-dependent gene regulation (Fig. 4). The production of NAD^+ in the nucleus is controlled by the nuclear NAD^+ synthase nicotinamide mononucleotide adenylyltransferase-1 (NMNAT-1), whereas the degradation of PAR is mediated by poly (ADP-ribose) glycohydrolase (PARG) [2,59]. NMNAT-1 not only produces NAD^+ for use by PARP-1, but it also stimulates PARP-1 activity and binds to PAR, thereby regulating PARP-1-dependent outcomes [60•]. The catabolism of PAR polymers by PARG occurs rapidly in vivo to yield monomers of ADP-ribose (ADPR). This may: (1) inhibit PAR-dependent processes, (2) re-set PAR-dependent processes so that continued regulation can occur, or (3) generate ADPR, which may have signaling functions in the nucleus [1–3,61]. With respect to the latter, ADPR has recently been shown to be a ligand for the macro domain of macroH2A1.1, but not the 1.2 splice variant [62]. Although the functional consequences of this are unknown, it may represent a mode of chromatin-dependent nuclear signaling.

Conclusions

The available data indicate that PARP-1 regulates transcription in perhaps as many as four modes: (1) as a modulator of chromatin structure by binding to nucleosomes, modifying histone proteins, or regulating the composition of chromatin, (2) as an enhancer-binding factor that functions in a manner similar to classical sequence-specific DNA-binding activators or repressors, (3) as a transcriptional coregulator that functions in a manner similar to classical coactivators and corepressors, and (4) as a component of transcriptional insulators. Although recent studies have clarified some of the molecular details of these different modes of regulation, a unified model for the regulation of gene expression by PARP-1 remains elusive. Further studies examining the generality of these types of regulation, their interrelationships, and how they are regulated by cellular signaling pathways are needed.

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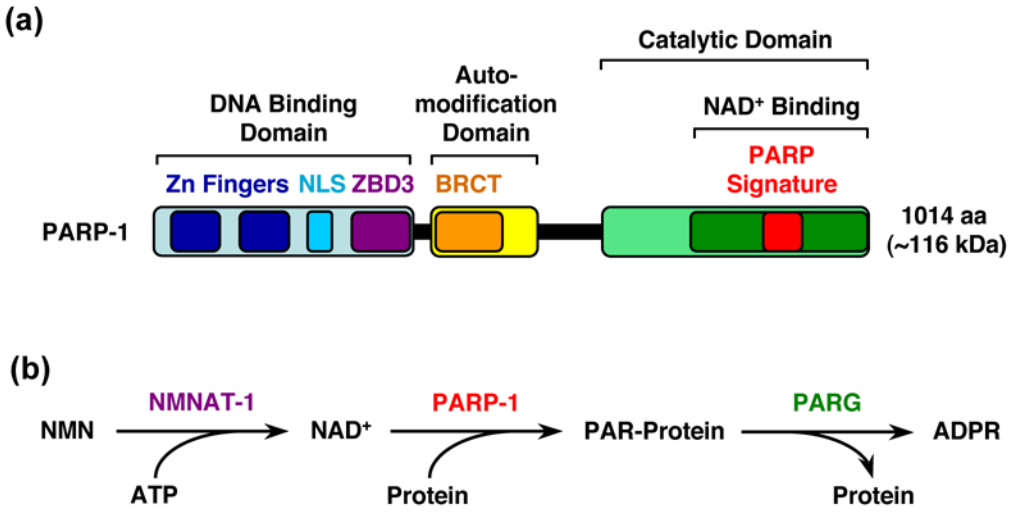

Figure 1. Schematic representation of PARP-1's structural and functional organization and the reactions in the PARP-1-dependent protein PARylation pathway

(a) PARP-1 has three major structural and functional domains: (1) an amino-terminal DNA binding domain containing two zinc finger motifs (Zn fingers), a nuclear localization signal (NLS), and a recently identified third zinc-binding domain (ZBD3), (2) a central automodification domain containing a BRCA1 C-terminus-like (BRCT) motif, and (3) a carboxyl-terminal catalytic domain containing an NAD^+-binding domain and a highly conserved "PARP signature" motif that defines the PARP superfamily of proteins. **(b)** The following reactions occur in the PARP-1-dependent protein PARylation pathway: (1) NMNAT-1 synthesizes NAD^+ from nicotinamide mononucleotide (NMN) and ATP, (2) PARP-1 polymerizes linear or branched chains of ADP-ribose (ADPR) from donor NAD^+ molecules on target proteins, and (3) PARG hydrolyzes the chains of poly(ADP-ribose) (PAR) to release free ADPR.

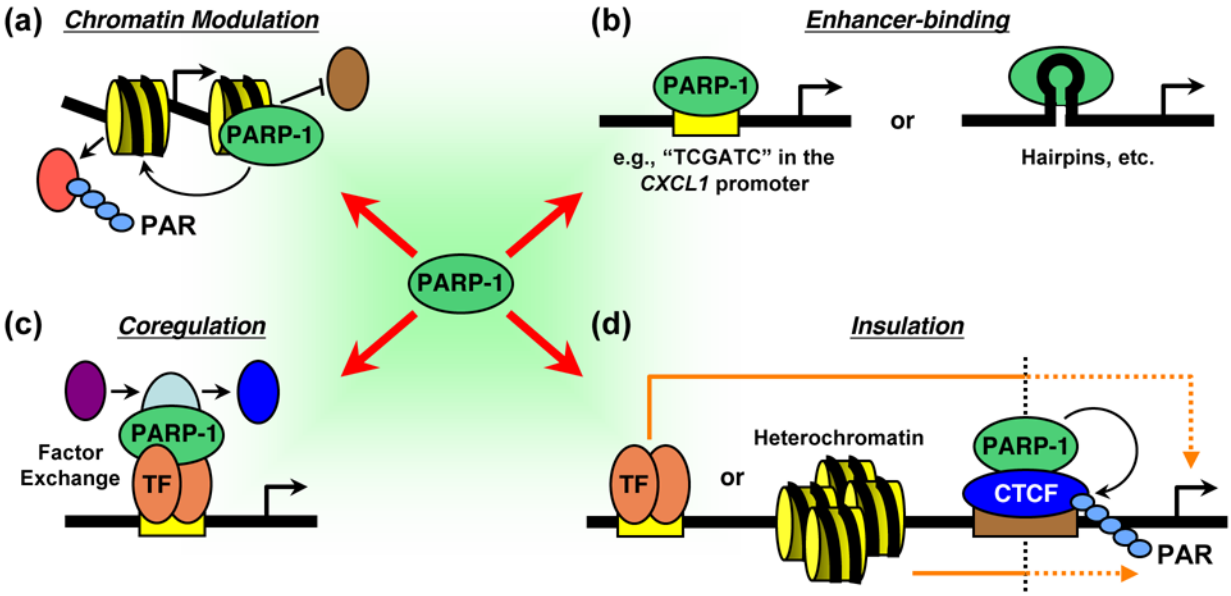

Figure 2. Multiple modes of transcriptional regulation by PARP-1

PARP-1 regulates transcription in perhaps as many as four modes, as indicated. **(a)** PARP-1 can modulate chromatin structure by binding to nucleosomes, modifying histone proteins, or regulating the composition of chromatin. **(b)** PARP-1 can act as an enhancer-binding factor that functions in a manner similar to classical sequence-specific DNA-binding activators or repressors. In this mode, PARP-1 may bind to specific sequences or structures in the DNA. **(c)** PARP-1 can function as a transcriptional coregulator in a manner similar to classical coactivators and corepressors. In this mode, PARP-1 may function as a promoter-specific "exchange factor" that promotes the release of inhibitory factors and the recruitment of stimulatory factors during signal-regulated transcriptional responses. TF, DNA-binding transcription factor **(d)** PARP-1 can function as a component of insulators, which act to limit the effects of enhancers on promoters or by preventing the spread of heterochromatin. In this mode, the PARylation of CTCF by PARP-1 is likely to play a role in the maintenance of insulator function.

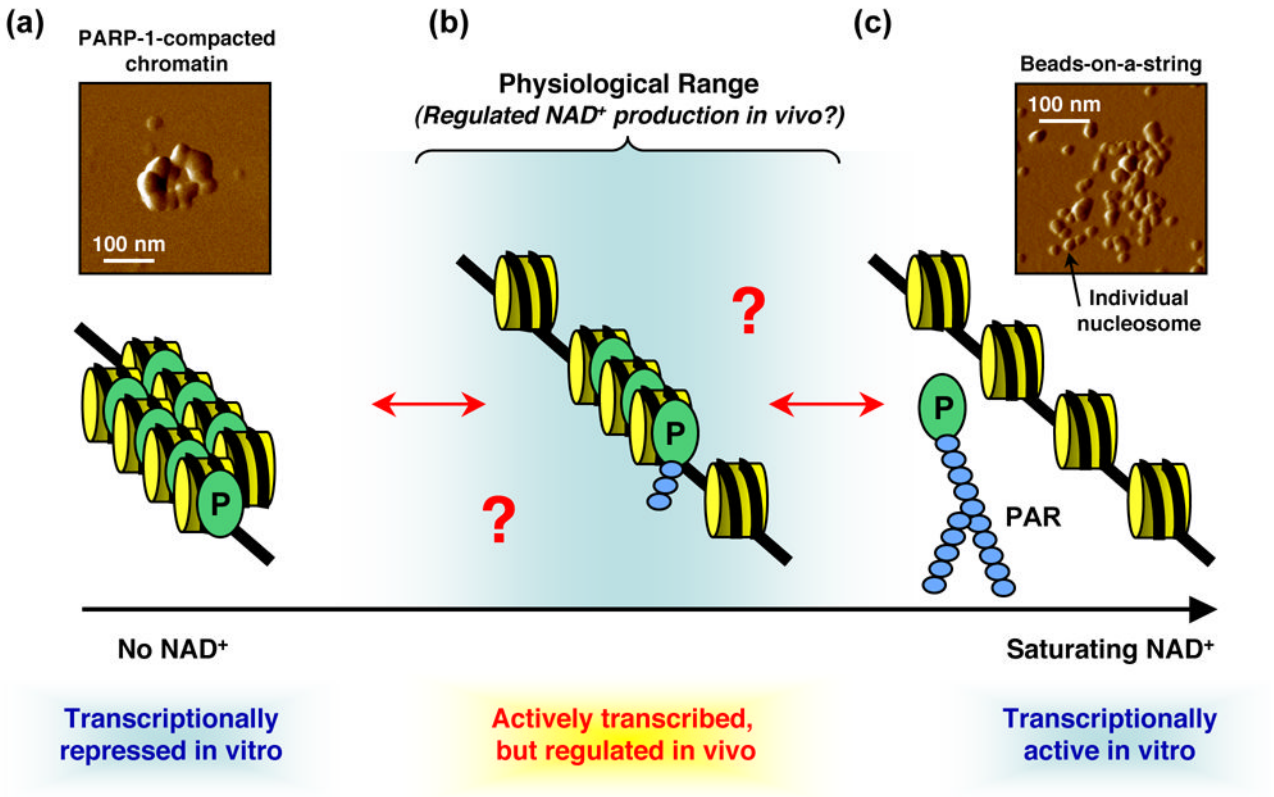

Figure 3. Regulation of chromatin structure by PARP-1

Schematic representation of the effects of PARP-1 on chromatin structure in the presence of different levels of NAD^+. **(a)** In biochemical assays, saturated binding of PARP-1 (P) to nucleosomes in the absence of NAD^+ and promotes the compaction of nucleosomal arrays into higher order structures. Inset: PARP-1-dependent compaction of a single molecule of reconstituted chromatin assembled from an ~11 kb plasmid, as visualized by atomic force microscopy (similar to the images described by Wacker et al., 2007 [6•]). A length scale bar is shown. **(b)** Hypothetical model of an intermediate chromatin state at physiological levels of NAD^+ that might be found in vivo, although the actual structure is currently unknown. In this state, oligo(ADP-ribosyl)ation of PARP-1 may have a regulatory effect without promoting the dissociation of PARP-1 from chromatin. **(c)** In biochemical assays with saturating amounts of NAD^+, PARP-1 automodifies and releases from the chromatin, leading to decompaction. Inset: NAD^+-dependent decompaction ("beads-on-a-string" conformation) of a single molecule of PARP-1-containing chromatin assembled from an ~11 kb plasmid, as visualized by atomic force microscopy (similar to the images described by Wacker et al., 2007 [6•]). A length scale bar is shown. PAR, poly(ADP-ribose).

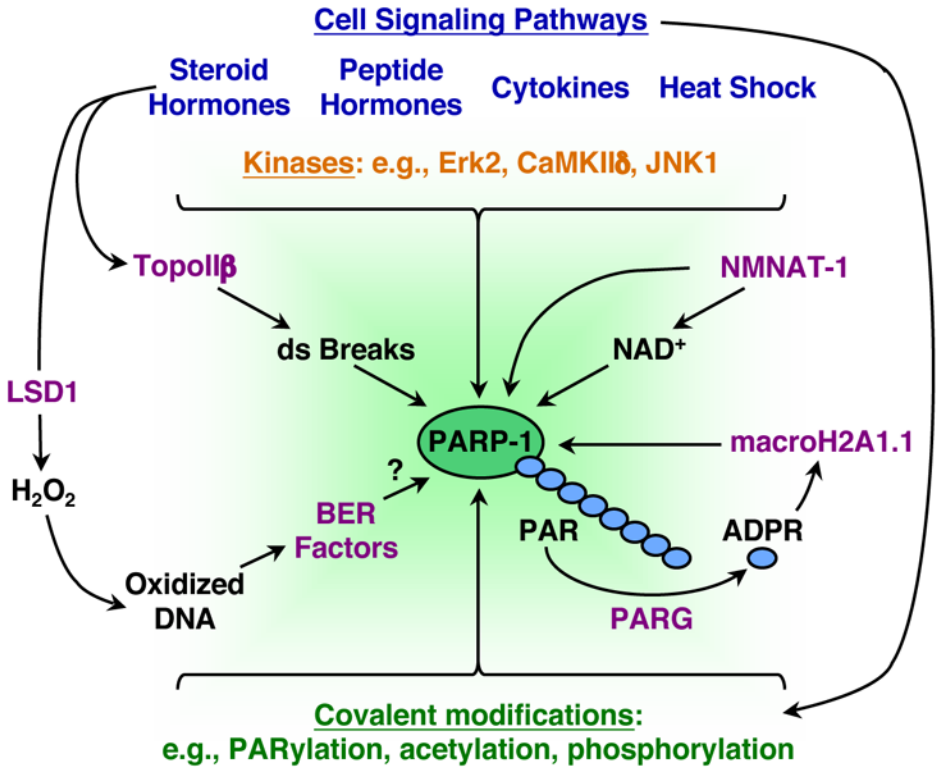

Figure 4. Signaling and regulation in PARP-1-dependent gene expression pathways

Schematic representation of some of the many signaling and regulatory inputs that affect PARP-1-dependent transcriptional outcomes. Mediating signals include hormones, cytokines, heat shock, and intracellular kinases (e.g., CaM kinase IIδ and Erk2). One endpoint of these signaling pathways is the post-translational modification of PARP-1 by autoPARylation, acetylation, and phosphorylation. NAD^+ synthesis by NMNAT-1 and PAR catabolism by PARG represent additional points of control. In addition to producing NAD^+ for use by PARP-1, NMNAT-1 also stimulates PARP-1 catalytic activity. The degradation of PAR polymers by PARG yields monomers of ADP-ribose (ADPR), a ligand for the macro domain of macroH2A1.1, which may have signaling functions in the nucleus. Transcription-induced DNA damage may also affect PARP-1's gene-regulatory activities at target promoters. For example, estrogen signaling can induce transient TopoIIβ-dependent double strand (ds) DNA breaks, which may promote the recruitment and activation of PARP-1. Likewise, estrogen-induced demethylation of histones by LSD1 generates H_2O_2 that can oxidize promoter DNA and promote the recruitment of components of the base excision repair (BER) machinery and TopoIIβ, which may in turn promote the recruitment and activation of PARP-1.