CHAPTER 7

Dynamic Interaction between PARP-1, PCNA and p21$^{waf1/cip1}$

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Abstract

Poly(ADP-ribose) polymerase (PARP-1) plays a crucial role in DNA repair and interacts with many DNA replication/repair factors, including the proliferating cell nuclear antigen (PCNA), a protein involved in many DNA transactions. The association between these proteins in vitro results in the inhibition of PARP-1 activity and of PCNA-dependent DNA synthesis carried out by DNA polymerase δ. In vivo, the interaction of the two proteins has been shown to increase after DNA damage. The activity of PCNA is regulated by p21$^{waf1/cip1}$, which binds the interdomain connector loop of PCNA in the same region involved in the interaction of PCNA with DNA polymerase δ. This feature enables p21 to compete with DNA polymerase δ to regulate the differential inhibition of DNA replication vs. DNA repair. The finding that PARP-1 is associated with both PCNA and p21 suggests a possible cooperation of PARP-1 and p21 in regulating the functions of PCNA during DNA replication/repair.

Abbreviations

BER, base excision repair; DNA-PK, DNA-dependent protein kinase; DSB, double strand break; MNNG, N-methyl-N'-nitro-N-nitrosoguanidine; MRC, multiprotein DNA replication complex; NER, nucleotide excision repair; PAR, poly(ADP-ribose); PARP-1, poly(ADP-ribose) polymerase-1; PCNA, proliferating cell nuclear antigen; p21, p21$^{waf1/cip1}$; pol δ, DNA polymerase δ; SSB, single strand break; WRN, Werner syndrome protein.

Introduction

PARP-1 and PCNA share the property of working in association with a number of factors that are involved in the regulation of DNA metabolism. This feature legitimates the search for a physical interaction between PARP-1 and PCNA, which in fact has been demonstrated by in vitro assays and by coimmunoprecipitation experiments. Since both PARP-1 and PCNA play an active role in DNA repair and replication, a functional association between them has been postulated. Indeed, an inhibitory effect on the respective enzymatic activities, mediated by their association, was reported. Finally, due to the relevant role of p21$^{waf1/cip1}$ in regulating the activity of PCNA, the existence of an interplay between PCNA-PARP-1, PCNA-p21 and p21-PARP-1 interactions was investigated.

PARP-1 Interacts with DNA Repair/Replication Proteins

PARP-1 catalyzes the conversion of β-NAD$^+$ into ADP-ribose to produce polymers of ADP-ribose covalently bound to nuclear acceptors, including PARP-1 itself. The evidence for an active role of PARP-1 in DNA metabolism is supported by the observations that in vitro the

Poly(ADP-Ribosyl)ation, edited by Alexander Bürkle.

activity of DNA polymerases is modulated by poly(ADP-ribosylation)[1,2] and that PARP-1 is present in multiprotein DNA replication complexes (MRC),[2-4] where it regulates the recruitment of some components of the DNA synthesome.[2] When reconstituted systems were used, many potential acceptors of poly(ADP-ribose) (PAR) were identified; subsequently, several in vivo poly(ADP-ribosylated) proteins involved in DNA metabolism were found, including some factors that regulate chromatin structure, such as histones[5] and DNA topoisomerases I[6] and II.[7] In this respect, it has been shown that poly(ADP-ribosylation) by PARP-1 contributes to regulate the catalytic activity of topoisomerase I[8,9] and the expression of topoisomerase IIβ.[10]

The interaction between PARP-1 and other proteins is also mediated by the noncovalent binding of poly(ADP-ribose) through a canonical PAR-binding domain.[11] The PAR-binding consensus sequence is present in a family of proteins involved in DNA damage recognition and repair, including XPA, XRCC1, DNA ligase III and DNA-PK.[11] This motif has not been found in the aminoacid sequence of PCNA but is present at the C-terminus of p21,[11] where it coincides with the residues involved in its binding to the interdomain connector loop of PCNA.[12,13] By a proteomic approach, heterogeneous nuclear ribonucleoproteins have been identified among the proteins that bind poly(ADP-ribose).[14]

After the pioneering work of Shall and coworkers[15] reporting the negative effect of PARP inhibition on DNA repair, a large body of evidence supported the definition of PARP-1 as a guardian of the genome,[16] thus including this protein in the category of DNA damage-sensor molecules.[17,18] Recently, the generation of PARP-1-deficient mice allowed the definition of a more precise correlation between PARP-1 activity and DNA repair (reviewed in ref. 19). PARP-1 is mainly involved in the Base Excision Repair (BER) pathway,[20-22] where it interacts with other components of the multiprotein repair complex, such as XRCC1, DNA ligase III and DNA polymerase β.[23] Interestingly, the recruitment of DNA ligase III to DNA single strand breaks (SSB) is mediated by a zinc finger domain which is homologous to that of PARP-1. This feature can enable DNA ligase III to displace PARP-1 from the SSB, thus rendering DNA accessible to repair protein.[24,25] An involvement of PARP-1 in the Nucleotide Excision Repair (NER) pathway has also been reported.[26]

The surveillance network against DNA damage implies the interaction of PARP-1 with other factors. The interaction of PARP-1 with p53 has been widely described, thus supporting the existence of cooperation between these proteins in maintaining genome integrity (see Chapter 6). PARP-1 acts in concert with Werner syndrome protein (WRN), a protein involved in DNA replication and repair, which interacts directly with PARP-1[27-29] and with PCNA.[30] It has been recently shown that PARP-1, WRN and Ku70/80, which is a component of DNA-PK holoenzyme, are stably associated.[31] PARP-1 shares with Ku80 the ability to recognize and bind DNA double strand breaks (DSB), it stimulates the activity of DNA-PK and is associated with it;[32,33] on the contrary, DNA-PK suppresses PARP activity, possibly by competing for the binding to DNA ends.[34] The generation of double mutants for PARP-1/Ku80 revealed that the functions of both proteins are essential for DSB repair during mouse embryogenesis.[35] PARP-1 was described to act synergistically also with another factor involved in the response to DNA strand breaks, i.e., ATM.[36,37]

PCNA: A Protein with Many Partners

PCNA is a ring-shaped homo-trimeric protein[38] that functions on DNA as a clamping platform to recruit proteins involved in DNA metabolism.[39] During DNA replication, PCNA is loaded onto DNA by the replication factor C (RFC), and then it clamps DNA polymerase δ (pol δ) to the template (for a review see ref. 40). In the lagging strand, PCNA interacts also with other proteins, such as Flap endonuclease FEN-1,[41] which removes RNA primers, and DNA ligase I,[42] which seals newly synthesized DNA fragments.[43] PCNA plays a role in chromatin assembly through the binding to CAF-1[44] and the interaction with DNA-5'-cytosine methyl transferase (DNAMT).[45,46] An active role of PCNA during post-replication repair is supported by a number

of reports indicating its interaction with mismatch repair proteins, i.e., MSH3 and MSH6,[47] the uracil-DNA glycosylase 2,[48] and the cyclin-like uracil-DNA glycosylase.[49]

The growing list of proteins interacting with PCNA includes DNA polymerases β,[50] η,[51] ι,[52] κ[53] and λ,[54] terminal nucleotidyl transferase,[55] the Werner syndrome helicase,[30] AP endonucleases 1 and 2,[56,57] DNA glycosylase MYH,[58] the transcription factors Y-box binding protein[59] and p300,[60] the histone deacetylase HDAC,[61] the apoptotic proteins MCL1[62] and ING1,[63] and the cell cycle regulator Cdc25C.[64] Recently, by proteomic- and genomic-based strategies, new PCNA-interacting proteins have been discovered, i.e., CHL12, involved in chromosome cohesion,[65] and the 5'-3' DNA helicase RRM3.[66]

PCNA partners, including the CDK inhibitor p21, interact with the interdomain connector loop of PCNA through a motif of 8 aminoacids (QxxM/L/IxxFF/FY).[67] PARP-1 shows a putative PCNA-binding consensus sequence (QDLIKMIF) at the position 669 within the catalytic domain that is essential for the conversion of NAD^+ into ADP-ribose.

PCNA is present in the cell both as a free/detergent-soluble protein, and a chromatin-bound/detergent-insoluble form which, encircling DNA, is directly involved in DNA synthesis. The native PCNA trimer has three potential binding sites,[67] thus each PCNA ring may interact with more than one protein at the same time. In this respect, we have recently proposed a mechanism by which PCNA trimers bound to DNA during S phase are organized as distinct pools able to bind different partners in a mutually exclusive manner.[68] During DNA repair, the multiple interactions established by PCNA could be regulated by p21 in a disassembly and/or recycling process of PCNA molecules at repair sites.[69,70]

p21 Regulates the Activity of PCNA

The cyclin-dependent kinase (CDK) inhibitor $p21^{CDKN1A}$ (also known as $p21^{WAF1/Cip1}$) plays an important role in several cellular pathways in response to intracellular and extracellular stimuli. In particular, p53-dependent induction of p21 after DNA damage leads to inhibition of cell cycle progression and DNA replication. In addition, p21 is clearly involved in other processes like senescence, differentiation, and regulation of gene expression.[71,72]

Cell cycle arrest is performed by p21 not only through CDK inhibition, but also by direct binding to PCNA, thereby interfering with PCNA-dependent DNA synthesis.[73,74] The dual effect on cell cycle regulatory proteins is mediated in the p21 sequence via distinct interaction sites for cyclin-Cdk complexes and for PCNA.[73,74] Binding of p21 to PCNA occurs at the interdomain connector loop, i.e., the same region involved in the binding of several PCNA-interacting proteins.[67] For some of them (e.g., DNA pol δ, FEN-1, DNAMT), binding of p21 has been shown to result in their displacement from PCNA,[75] thereby inhibiting DNA replication.[76] In contrast, p21 does not inhibit PCNA-dependent DNA repair.[77,78] Several lines of evidence suggest that p21 is actively involved in DNA repair; in fact, human p21-null cells have been shown to be more sensitive to DNA damage, and to be deficient in DNA repair.[70,79,80]

Recent work by our group has shown that in vitro p21 is also able to compete with PARP-1 and displace it from the interdomain connector loop of PCNA.[81] In vivo, after MNNG-induced DNA damage, p21 interacts with PARP-1, but not with chromatin-bound PCNA, i.e., the form involved in DNA repair.[81] These results suggest that PARP-1 may sequester p21, probably to avoid an untimely interaction with PCNA, which would inhibit DNA repair.

Effect of the Interaction between PARP-1 and PCNA

We have recently shown that PARP-1 associates in vitro and in vivo with PCNA in HeLa cells and human fibroblasts.[81] A typical pattern of coimmunoprecipitation is reported in Figure 1, which also shows the increase in the amount of coimmunoprecipitated PARP-1 and PCNA in MNNG-treated HeLa cells, thus suggesting that this association may play a role in the cell response to DNA damage by alkylating agents. This feature is not strictly mediated by poly(ADP-ribose) chains, since experiments carried out in the presence of 3-aminobenzamide,

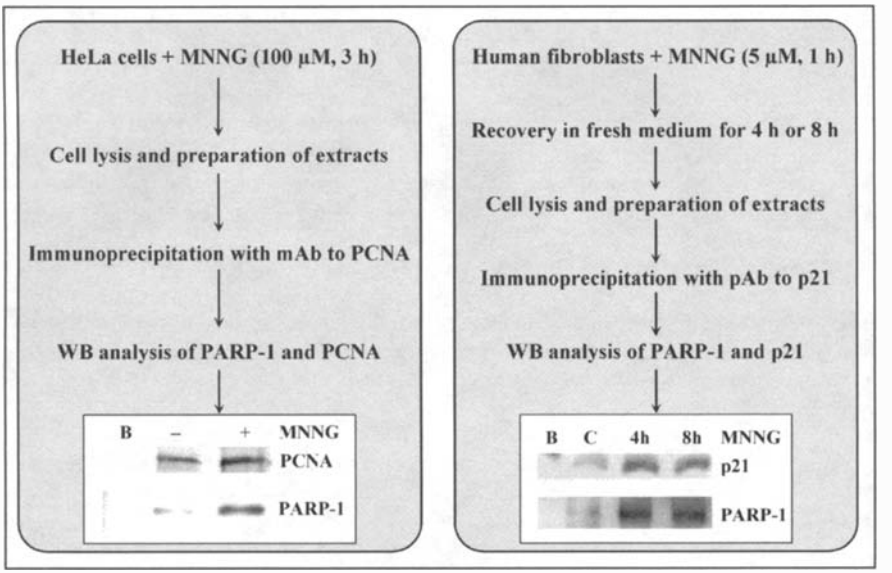

Figure 1. Left panel) Coimmunoprecipitation of PCNA and PARP-1 from control and MNNG-treated HeLa cells synchronized in S phase. Immunoprecipitation was obtained by the mAb PC10 to PCNA. As a negative control, the procedure was carried out with mouse IgG (B). Right panel) Coimmunoprecipitation of p21 and PARP-1 from control (C) and MNNG-treated human fibroblasts. Immunoprecipitation was obtained by a polyclonal antibody to p21. As a negative control, the procedure was carried out with rabbit IgG (B). A typical result is shown. Experimental procedures are described in reference 81.

an inhibitor of poly(ADP-ribosylation), revealed that the association occurred also when PARP-1 activity was suppressed.[81]

We observed that PARP-1 affects PCNA-dependent pol δ activity in vitro and that this effect is more evident in the presence of an excess of PARP-1. From this finding, it is tempting to speculate that the association of PCNA with PARP-1 occurs at the same region involved in the interaction of PCNA with pol δ. Since such interaction is essential for processive DNA synthesis, PARP-1 could act as a negative regulator of PCNA-dependent pol δ activity when replicative DNA synthesis has to be inhibited, e.g., under damage conditions. On the other hand, we have shown that PCNA inhibits PARP-1 activity in vitro, possibly through the physical interaction between the putative PCNA-binding sequence located within the catalytic domain of PARP-1. This feature suggests that PCNA could regulate negatively PARP-1 activity, thus allowing the inhibition of poly(ADP-ribosylation) reactions, to avoid an excessive consumption of NAD^+ or the inappropriate modification of the structure and function of crucial proteins.

The region of the interdomain connector loop of PCNA that is involved in the association with pol δ is identical to the sequence interacting with the C-terminus of p21.[12,13,75] Competition between pol δ and p21 for PCNA bindiÇO has been proposed to regulate the differential inhibition of DNA replication vs. DNA repair.[40,69] Interestingly, we have demonstrated that in vitro and in vivo the PCNA-binding region of p21 is also responsible for the direct association with PARP-1.[81] As suggested by coimmunoprecipitation (Fig. 1) and pull-down data,[81] PARP-1 could compete with the C-terminal region of p21 for the binding to the interdomain connector loop of PCNA. Our findings showing that PARP-1 binds both PCNA and p21, and that both interactions increase upon DNA damage, suggest that in vivo PARP-1, PCNA and p21 undergo a dynamic exchange of partners to regulate PCNA functions during DNA replication/repair. A dynamic interaction of PCNA with its partners has also been demonstrated for

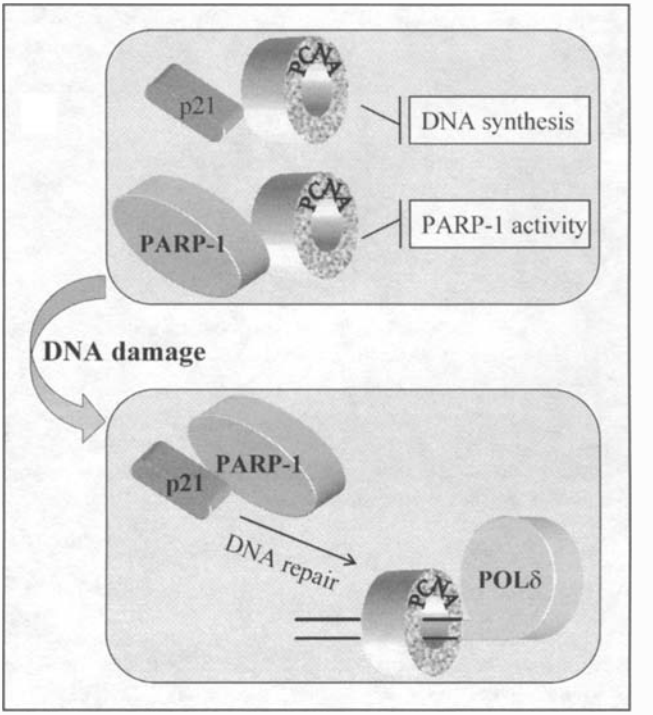

Figure 2. Dynamic association between PARP-1, PCNA and p21. Upper panel) The association of PCNA with either p21 or PARP-1 prevents its interaction with DNA replication/repair factors and, by consequence, inhibits PCNA-dependent DNA synthesis. PARP-1 activity is in turn inhibited by the association with PCNA. After DNA damage (lower panel), these proteins are reassembled. p21 is sequestered by PARP-1, thus making PCNA free to associate to DNA and to recruit crucial proteins, e.g., pol δ.

the association with pol δ and DNA ligase I.[68] In conclusion, these observations prompt us to propose a model in which, from one side, PARP-1 may inhibit PCNA-dependent DNA replication, while from the other side, sequestration of p21 by PARP-1 could enable PCNA to be recruited to DNA repair sites (Fig. 2).

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