Minireview

The diverse spectrum of sliding clamp interacting proteins

Jonathan B. Vivona, Zvi Kelman*

University of Maryland Biotechnology Institute, Center for Advanced Research in Biotechnology, 9600 Gudelsky Drive, Rockville, MD 20850, USA

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Abstract DNA polymerase sliding clamps are a family of ring-shaped proteins that play essential roles in DNA metabolism. The proteins from the three domains of life, Bacteria, Archaea and Eukarya, as well as those from bacteriophages and viruses, were shown to interact with a large number of cellular factors and to influence their activity. In the last several years a large number of such proteins have been identified and studied. Here the various proteins that have been shown to interact with the sliding clamps of Bacteria, Archaea and Eukarya are summarized.

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Key words: Cell cycle; DNA repair; DNA replication; Protein–DNA interaction; Protein–protein interaction

1. DNA sliding clamps

Originally, DNA sliding clamps (also known as DNA polymerase processivity factors) were identified as factors that endow the replicative polymerase with high processivity [1]. Although the best understood function for the sliding clamps is their essential role in chromosomal DNA replication, they have been implicated in a large number of other cellular processes. In *Escherichia coli*, the sliding clamp is the β subunit of DNA polymerase III holoenzyme; in Eukarya and Archaea it is the product of the proliferating cell nuclear antigen (PCNA) gene [2,3]. Although the primary amino acid sequences of the sliding clamps from the three domains of life are different, all have very similar three-dimensional structures [4,5]. Furthermore, although PCNA is a trimer and the β protein is a dimer, they are superimposable in three dimensions [2]. Each ring has similar dimensions and a central cavity large enough to accommodate a duplex DNA molecule [2,5]. The sliding clamps do not assemble themselves around DNA but are loaded onto DNA by a protein complex referred to as a clamp loader [6,7]. Following their assembly around double-stranded DNA, they can slide bidirectionally along the duplex [8,9].

Sliding clamps have no known enzymatic activity. They interact, however, with a large number of cellular factors and regulate their activity (Tables 1–3). Some of these factors are enzymes involved in DNA replication, recombination, and repair, in which the interactions with the clamps bring them to the DNA substrate and/or regulate their activity. Others (to date identified only in Eukarya) are cell cycle regulators whose interactions with PCNA influence cell cycle progression. It was also suggested that the ability of the clamps to slide along duplex DNA may function as a moving platform on which enzymes involved in DNA metabolism, but with low sequence specificity, can travel [10].

2. Sliding clamp interacting motifs

It was noted that many of the proteins that interact with eukaryal and archaeal PCNA contain a PCNA binding motif [11,12]. This motif is called the PCNA interacting protein box (PIP box). An alignment of the PIP boxes from a large number of proteins showed that it consists of the sequence Qxxhxxaa, where 'x' represents any amino acid, 'h' represents residues with moderately hydrophobic side chains (L, I, or M), and 'a' represents residues with hydrophobic, aromatic side chains (F, H, or Y), followed by a non-conserved sequence containing basic amino acids. It is clear, however, that other regions of the proteins can also participate in PCNA binding (e.g. [13]).

A PCNA interacting motif, which is different from the PIP box, has been identified using a random peptide display library [14]. The motif contains a highly conserved pair of KA residues, together with additional conserved amino acids, and thus was termed the KA box. Although this motif has been identified in a large number of proteins, including several that were shown to interact with PCNA [14], to date only limited studies have been performed to demonstrate a direct role of the motif in PCNA binding.

A putative conserved motif, which is found in proteins interacting with the β subunit, has been identified [15]. The motif consists of the sequence QL(S/D)LF and was identified in the sequence of bacterial enzymes belonging to the C and Y families of DNA polymerases and in the sequence of MutS [15]. The function of the domain in the interactions between β and other proteins remains to be seen. Interestingly, although Archaea do not have a homologue of the bacterial β subunit, this motif has also been found in the sequence of archaeal members of family B DNA polymerases [15]. The role(s), if any, played by this domain in the archaeal polymerases remains to be determined.

3. Sliding clamp interacting proteins

Over the last decade, the sliding clamps of Bacteria, Ar-

*Corresponding author. Fax: (1)-301-738 6255.
E-mail address: kelman@umbi.umd.edu (Z. Kelman).

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Table 1
PCNA interacting proteins in Eukarya

Protein	Effects of interactions with PCNA	Interacting region		Methods by which interactions were demonstrated	Selected references
		PCNA	Protein		
DNA replication					
Initiation					
Cell division cycle 6 (Cdc6)[a]				Yeast two-hyb	[30]
Elongation					
DNA polymerase δ (Pol δ)	Stimulation of polymerase activity	C-ter and center region	Multiple subunits	Co-IP, GST pull-down, yeast two-hyb, functional assay in vitro, functional assay in vivo, gel filtration, ELISA, far-Western, PCNA column retention	[34–42]
DNA polymerase ε (Pol ε)	Stimulation of polymerase activity	C-ter and center region		Functional assay in vitro, functional assay in vivo	[41,43–45]
Replication factor C (RFC)	Loading of PCNA onto DNA	C- and N-ter	Multiple subunits	Co-IP, functional assay in vitro, functional assay in vivo, SPR, gel mobility shift assay, molecular modeling	[46–50]
Replication protein A (RPA)				PCNA column retention	[51]
Okazaki fragment maturation					
DNA ligase I	Stimulates ligase activity	Center region	N-ter	Co-IP, GST pull-down, functional assay in vitro, functional assay in vivo, gel filtration	[52–54]
Flap endonuclease 1 (Fen-1)	Stimulates Fen-1 activity	Center region	C-ter	Co-IP, GST pull-down, yeast two-hyb, functional assay in vitro, functional assay in vivo, SPR, far-Western blot	[55–59]
Post-replicative processes					
Chromatin assembly factor-1 (CAF-1)	Promotes chromatin assembly	Center region	N-ter	Co-IP, GST pull-down, yeast two-hyb, co-localization in vivo, functional assay in vitro	[60,61]
Chromosomal transmission fidelity 7 (Ctf7)				Functional assay in vivo	[62]
Chromosomal transmission fidelity 18 (Ctf18)[a]	Loading of PCNA onto DNA			Co-IP, PCNA column retention, molecular modeling, functional assay in vitro	[19,50], V. Bermudez and J. Hurwitz, personal communication
DNA cytosine-methyltransferase (DNMT)	Stimulation of DNMT activity	C-ter and center region	N-ter	Co-IP, GST pull-down, functional assay in vitro, co-localization in vivo, peptide binding, SPR, PCNA column retention	[63,64]
DNA repair and recombination					
Apurinic/apyrimidinic endonuclease 1 (APE1)	Stimulates APE1 exonuclease and phosphodiesterase activities	C-ter and center region	C-ter	Co-IP, yeast two-hyb, PCNA column retention, functional assay in vitro, gel filtration	[65,66]
Apurinic/apyrimidinic endonuclease 2 (APE2)	Stimulates APE2 activities		C-ter	Co-IP, co-localization in vivo, peptide binding, PCNA column retention, functional assay in vitro	[66,67]
DNA polymerase β (Pol β)			Center region	Co-IP, yeast two-hyb, far-Western	[68]
DNA polymerase λ (Pol λ)	Stimulation of polymerase activity		C-ter	GST pull-down, functional assay in vitro, protein pull-down assay, electrophoretic mobility shift assay	[69,70]
DNA polymerase η (Pol η)	Stimulation of polymerase activity		C-ter	GST pull-down, yeast two-hyb, functional assay in vitro, functional assay in vivo, gel filtration	[71,72]
DNA polymerase κ (Pol κ)	Stimulation of polymerase activity			GST pull-down, functional assay in vitro	[73]
DNA polymerase ι (Pol ι)	Stimulation of polymerase activity			Functional assay in vitro, gel filtration	[74]
Growth arrest and DNA damage α (Gadd45α)	Hinders growth arrest and apoptosis	N-ter and center region	C-ter	Co-IP, yeast two-hyb, functional assay in vivo, ELISA	[75–77]
Growth arrest and DNA damage β (Gadd45β)	Hinders growth arrest and apoptosis	N-ter and center region	C-ter	Co-IP, yeast two-hyb, functional assay in vivo, ELISA	[75,78]
Growth arrest and DNA damage γ (Gadd45γ)	Hinders growth arrest and apoptosis	N- and C-ter and center region	C-ter	Co-IP, yeast two-hyb, functional assay in vivo	[79]
Ku70/Ku80 complex				Co-IP, co-localization in vivo	[80]
MutL homologue 1 (MLH1)				Yeast two-hyb	[81]
MutS homologue 2 (MSH2)[a]				Yeast two-hyb	[81]
MutS homologue 3 (MSH3)			N-ter	GST pull-down, co-localization in vivo, functional assay in vitro, functional assay in vivo, far-Western	[82,83]
MutS homologue 6 (MSH6)			N-ter	GST pull-down, co-localization in vivo, functional assay in vitro, functional assay in vivo, far-Western	[82,83]
MutY homologue (MYH)		Center region	C-ter	Co-IP, GST pull-down, functional assay in vivo	[84,85]
Radiation-sensitive mutant 5 (RAD5)	Ubiquitination of PCNA; role in DNA repair			Yeast two-hyb, functional assay in vitro, functional assay in vivo	[86]
Radiation-sensitive mutant 18 (RAD18)	Ubiquitination of PCNA; role in DNA repair			Yeast two-hyb, functional assay in vitro, functional assay in vivo	[86]
Ubiquitin conjugating enzyme 9 (UBC9)	Ubiquitination of PCNA; SUMO conjugation of PCNA; role in DNA repair			Yeast two-hyb, functional assay in vitro, functional assay in vivo	[86]
Ribosomal DNA recombination mutation 3 (RRM3)			N-ter	PCNA pull-down, yeast two-hyb	[18]
Uracil-DNA glycosylase (UDG)			N-ter	Co-IP, peptide binding	[87]
Werner syndrome (WS)		C-ter and center region	N-ter	Co-IP, GST pull-down, functional assay in vivo, peptide binding, sucrose gradient	[88]
Xeroderma pigmentosum G (XPG)	Needed for nucleotide excision repair	Center region	C-ter	GST pull-down, functional assay in vivo, PCNA column retention	[58]
Regulatory proteins					
p21	Inhibits PCNA-dependent DNA replication	C-ter and center region	C-ter	Co-IP, co-localization in vivo, functional assay in vitro, functional assay in vivo, gel filtration, SPR, ELISA, peptide binding, glycerol gradient, three-dimensional structure	[13,89–93]
p57	Inhibits cell growth		C-ter	Co-IP, GST pull-down, yeast two-hyb, functional assay in vitro, functional assay in vivo	[94]
p300	Stimulation of DNA synthesis in vitro	C-ter		Co-IP, GST pull-down, co-localization in vivo	[24]
Cyclin D	Inhibits cell growth	N- and C-ter		Co-IP, GST pull-down, functional assay in vitro	[95,96]
Cyclin-dependent kinase 2 (Cdk2)	Stimulates the phosphorylation of replication proteins by Cdk2–cyclin A complex	C-ter		Co-IP, GST pull-down, functional assay in vitro, SPR, PCNA column retention	[51,97]
Cyclin-dependent kinase 4 (Cdk4)				PCNA column retention	[51]
Cyclin-dependent kinase 5 (Cdk5)				PCNA column retention	[51]
Other proteins					
p15				Yeast two-hyb	[98]
Cell division cycle 24 (Cdc24)			N-ter	Co-IP	[99]
DNA helicase II (NDH II)				PCNA column retention	[51]

Table 1 (*Continued*).

Protein	Effects of interactions with PCNA	Interacting region		Methods by which interactions were demonstrated	Selected references
		PCNA	Protein		
HLA-derived peptide				Yeast two-hyb, co-localization in vivo, functional assay in vivo, peptide binding	[100]
Inhibitor of growth 1 (ING1)	Needed for apoptosis		N-ter	Co-IP, co-localization in vivo, glycerol gradient	[101]
Myeloid cell leukemia 1 (MCL1)		C-ter	Center region	Co-IP, yeast two-hyb	[102]
Pogo transposon		Center region	C-ter	Yeast two-hyb, ELISA, peptide binding	[11,34]
Polδ interacting protein 1 (PDIP1)	Stimulation of PCNA-dependent Polδ activity in vitro		C-ter	GST pull-down, yeast two-hyb, co-localization in vivo	[103]
Terminal deoxynucleotidyl-transferase (TdT)	Negative regulation of TdT activity	C-ter	DNA polymerase domain	Co-IP, yeast two-hyb, gel filtration	[104]
Topoisomerase I (Topo I)				PCNA column retention	[51]
Topoisomerase II (Topo II)				GST pull-down, co-localization	[105]

[a]The interactions with PCNA are likely to be indirect.

chaea, and Eukarya have been shown to interact with a large, and growing, number of cellular factors. To date, the largest number of proteins associated with sliding clamps are those binding to the eukaryotic PCNA (Table 1). These proteins can be divided into two main groups [10]. One group consists of proteins with well-defined enzymatic activities needed for nucleic acid metabolism. The second group consists of cell cycle regulators that play multiple roles in cell cycle progression and control. To date, in Bacteria and Archaea only enzymes have been shown to interact with the respective sliding clamps (Tables 2 and 3). It is possible that prokarya, with a simpler cell cycle, need fewer regulation points and thus the involvement of the clamp is not needed. Nevertheless, in all three domains the interactions between the clamps and diverse cellular factors play crucial roles for cell growth (Tables 1–3).

In this report a summary of an extensive literature search to identify all proteins reported to interact with the sliding clamps of the three domains of life is reported (Tables 1–3). Several of the interactions have been thoroughly studied while only limited information is available for others. Thus, in the tables, the various methods used to demonstrate the interactions are described. The interaction between PCNA and some of the proteins was reported based solely on a yeast two-hybrid screen or retention on a PCNA column. Although these studies have been included in the tables (to make them complete), readers are advised to be cautious.

Each table is divided into subsections based on the various cellular processes the sliding clamps are involved in. These subsections include proteins participating in DNA replication (including initiation, elongation, where DNA synthesis takes place, and maturation of the Okazaki fragments on the lagging strand), enzymes involved in post-replication processes, those involved in recombination and repair, and regulatory factors.

4. How many sliding clamp interacting proteins are there?

Extensive searches for proteins that interact with the archaeal and bacterial sliding clamps have begun only recently. However, based on searches for PIP and KA boxes and the β subunit binding motif, several hundred putative sliding clamp interacting proteins have been identified [14–18]. Some of the proteins originally identified using such in silico searches were later confirmed by biochemical studies. Thus, future studies will, no doubt, identify some of the proteins as authentic sliding clamp interacting factors. A different approach based on liquid chromatography and tandem mass spectrometry was also used to identify PCNA interacting proteins [19]. This approach has the potential to identify additional sliding clamp interacting proteins in the context of large complexes. Other approaches, such as the two-hybrid screen [20], may also lead to new clamp interacting proteins.

The sliding clamps of all three domains are similar in structure and function (most notably as processivity factors) and interact with similar cellular factors. Thus, studying the sliding clamp interacting protein in one system may suggest similar interactions in the others. Several such possible clamp interacting proteins are discussed below.

5. What can we learn by comparing sliding clamp interacting factors in the three domains of life?

In viruses and bacteriophages the sliding clamps were shown to interact with the transcription apparatus and to

Table 2
PCNA interacting proteins in Archaea

Protein	Effects of interactions with PCNA	Methods by which interactions were demonstrated	Selected references
DNA replication			
Elongation			
DNA polymerase B (Pol B)	Stimulation of polymerase activity	Co-IP, functional assay in vitro, GST pull-down	[20,26,106–109]
DNA polymerase D (Pol D)	Stimulation of polymerase activity	Co-IP, functional assay in vitro	[20,106]
Replication factor C (RFC)	Loading of PCNA onto DNA	Co-IP, yeast two-hyb, functional assay in vitro, gel filtration, three-dimensional structure, molecular modeling	[20,26,50,109–112]
Okazaki fragment maturation			
DNA ligase	Stimulation of polymerase activity	GST pull-down	[26]
Flap endonuclease (Fen-1)	Stimulates Fen-1 activity	GST pull-down, yeast two-hyb, functional assay in vitro	[26,113]
RNase HII		Yeast two-hyb	[20]
DNA repair and recombination			
DNA polymerase Y1 (Pol Y1)	Stimulation of polymerase activity	Functional assay in vitro	[114]
Radiation-sensitive mutant 2 (RAD2)		Yeast two-hyb	[20]
Uracil DNA glycosolase (UDG)		GST pull-down	[113]
XPF	Stimulation of XPF nuclease activity	Functional assay in vitro, GST pull-down	[115]

Table 3
β subunit interacting proteins

Protein	Effects of interactions with β subunit	Methods by which interactions were demonstrated	Selected references
DNA replication			
Initiation			
DnaA	Promotes DnaA ATP hydrolysis	Functional assay in vitro	[29]
Elongation			
DNA polymerase III (Pol III)	Stimulates polymerase activity	Protein gel shift assay, functional assay in vitro, gel filtration, SPR, kinase protection assay	[15,116,117]
γ complex	Loading β onto DNA	Gel filtration, kinase protection assay, SPR, crystal structure	[116–119]
Okazaki fragment maturation			
DNA ligase		Protein gel shift assay	[120]
DNA polymerase I (Pol I)	Stimulates polymerase activity	Protein gel shift assay, functional assay in vitro	[120]
DNA repair and recombination			
DNA polymerase II (Pol II)	Stimulates polymerase activity	Protein gel shift assay, functional assay in vitro, gel filtration	[120–122]
DNA polymerase IV (Pol IV)	Stimulates polymerase activity	Yeast two-hyb, functional assay in vitro, functional assay in vivo	[123,124]
DNA polymerase V (Pol V)	Stimulates polymerase activity	Functional assay in vitro	[125,126]
MutS		Protein gel shift assay, kinase protection assay	[120]

regulate gene expression (e.g. [21–23]). To date, only the transcriptional co-activator p300 was shown to interact with human PCNA (Table 1) [24]. It will be of great interest to determine whether additional components of the eukaryotic transcription machinery, or those of Bacteria and Archaea, interact with their respective sliding clamps.

Some interesting observations made in bacterial and archaeal systems may have important implications for future studies in Eukarya. In Eukarya it was shown that most of the proteins that participate in Okazaki fragment maturation (Fen-1, DNA ligase I, and Pol δ and ε) are associated with PCNA (Table 1) (reviewed in [25]). These interactions lead to a model of a sequential recruitment of these proteins to the lagging strand, via their interactions with PCNA, during its maturation to a continuous duplex DNA [25,26]. To date, one of the proteins needed for the process that has not been shown to interact with PCNA is RNase H. The observation that the archaeal RNase H protein binds PCNA (Table 2) [20] suggests that the eukaryotic protein may also bind PCNA. It will be of interest to investigate whether such an interaction exists.

DnaA is the bacterial origin binding protein and the functional homologue of the eukaryotic six subunit origin recognition complex (ORC) [27,28]. An interaction between DnaA and the β subunit has been reported (Table 3) [29]. It was also shown that this interaction regulates the initiation of chromosomal DNA replication in bacteria. To date an interaction between PCNA and archaeal or eukaryal initiator proteins has not been unequivocally demonstrated. However, eukaryotic PCNA was suggested to interact with the initiator protein Cdc6 [30]. In Eukarya, and possibly in Archaea, Cdc6p associates with ORC to promote the initiation process. To date, the interaction between the eukaryotic PCNA and Cdc6p was demonstrated only by a yeast two-hybrid screen and no interactions between the purified protein could be detected [30]. Thus the interactions may result from a technical artifact or may be mediated by an unidentified yeast protein. In addition, the large subunit of *Saccharomyces cerevisiae* ORC (Orc1) contains a PIP box (QDIMYNFF), though no direct interactions between ORC and PCNA have been reported. It is tempting to speculate, however, that an interaction between PCNA and either ORC or Cdc6p does exist, as is the case in Bacteria. Such an interaction may play a similar role by regulating the initiation process.

6. Sliding clamps from initiation to segregation

The sliding clamps of Eukarya and Archaea have been suggested to regulate the sequential recruitment of replication factors during DNA synthesis and Okazaki fragment maturation. The clamps left on DNA when DNA synthesis is completed are thought to regulate post-replication processes such as DNA methylation and chromatin assembly [31,32]. DNA metabolic processes share a high degree of similarity in Bacteria, Archaea, and Eukarya [28]. Therefore, proteins that associate with the sliding clamp in one system may have similar interactions in another. Thus one can suggest an attractive hypothesis to extend the role of the sliding clamps as a tool for sequential recruitment of cellular factors beyond DNA synthesis and post-replication processes. In Bacteria, the sliding clamp was shown to interact and regulate the activity of an initiation protein, DnaA; it may therefore be that a similar interaction exists in Eukarya. In addition, the eukaryotic PCNA was shown to interact with Ctf7 and DNA polymerase κ (Table 1), factors needed for cohesion establishment required for proper chromosome segregation [33]. It is therefore tempting to hypothesize that the non-enzymatic rings on DNA play essential roles in the cell cycle from the initiation of S-phase to mitosis.

7. Concluding remarks

In the past several years it has become apparent that although sliding clamps do not have any known enzymatic activity, they do play essential roles in all three domains of life. The proteins, originally identified by their ability to confer processivity to DNA polymerases, interact with a large number of cellular factors, modulating and regulating their activities. Although many such proteins have been identified and studied, the list is by no means complete and more clamp interacting proteins will be identified in the future.

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