The Pso4 mRNA Splicing and DNA Repair Complex Interacts with WRN for Processing of DNA Interstrand Cross-links*

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DNA interstrand cross-links (ICLs) are perhaps the most formidable lesion encountered by the cellular DNA repair machinery, and the elucidation of the process by which they are removed in eukaryotic cells has proved a daunting task. In particular, the early stages of adduct recognition and uncoupling of the cross-link have remained elusive principally because genetic studies have not been highly revealing. We have developed a biochemical assay in which processing of a DNA substrate containing a site-specific psoralen ICL can be monitored in vitro. Using this assay we have shown previously that the mismatch repair factor MutSβ, the nucleotide excision repair heterodimer Ercc1-Xpf, and the replication proteins RPA and PCNA are involved in an early stage of psoralen ICL processing. Here, we report the identification of two additional factors required in the ICL repair process, a previously characterized pre-mRNA splicing complex composed of Pso4/Prp19, Cdc5L, Plr1, and Spf27 (Pso4 complex), and WRN the protein deficient in Werner syndrome. Analysis of the WRN protein indicates that its DNA helicase function, but not its exonuclease activity, is required for ICL processing in vitro. In addition, we show that WRN and the Pso4 complex interact through a direct physical association between WRN and Cdc5L. A putative model for uncoupling of ICLs in mammalian cells is presented.

DNA interstrand cross-linking agents such as cyclophosphamide and mitomycin C are widely used as chemotherapeutic agents in the treatment of a broad spectrum of cancers. The clinical usage of these drugs has fueled an interest in elucidating the mechanisms of repair of interstrand cross-links (ICLs)† that still remain largely unresolved in eukaryotic cells. In prokaryotes two mechanisms of repair of these lesions have been identified. A major error-free pathway involves incision by the nucleotide excision repair (NER) pathway and a subsequent recombination gap filling step mediated by RecA (1–3). A minor error-prone pathway also requires incision by NER, while the gap filling step is accomplished via translesion synthesis performed by DNA polymerase II (4, 5). In each case the remaining monoaduct is removed by a second round of NER action. In budding yeast there appears to be a general conservation of these pathways in that a major mechanism involving NER and recombination has been identified (6–9), as well as a pathway involving the translesion polymerase Rev3 whose primary importance appears to occur in nonreplicating cells (9). In all eukaryotic cells examined double-strand breaks have been observed as intermediates of ICL repair (10–13) suggesting the possibility that recombination mechanisms may be required at more than one stage of this repair process. Mammalian cells have also been shown to employ two pathways of ICL repair. The minor pathway appears analogous to the Escherichia coli pathway in that it requires NER and presumably a translesion polymerase but not components of homologous recombination (14, 15). This pathway has also proved to be highly mutagenic in response to psoralen or mitomycin C adducts. The presumptive major pathway clearly requires homologous recombination, since mutations in genes such as XRCC1, XRCC2, and RAD51C result in severe sensitivity to ICL-inducing agents (16, 17). Mutants in the NER genes ERCC1 and XPF are also strikingly sensitive to these drugs; however, somewhat surprisingly other components of the NER pathway exhibit only mild sensitivity and have been shown not to be defective in the unhooking step of repair of nitrogen mustard ICLs in vivo (12). In general, cellular genetic studies have not been particularly revealing about the early stages of the major pathway of ICL repair in mammalian cells. Our prior biochemical studies have indicated a requirement for the mismatch repair factor MutSβ, the heterodimer Ercc1-Xpf, and replication protein A (RPA) in early recognition and uncoupling of psoralen ICLs (18–21). We have also shown that the recognition step by MutSβ is stimulated by PCNA. Consistent with these biochemical findings, it has been shown that Msh2 and Ercc1-Xpf act cooperatively in human cells to remove cisplatin ICLs and that these proteins interact as determined by co-immunoprecipitation experiments (22). Furthermore, recent findings in budding yeast have implicated a role for Msh2 and Exo I in repair of nitrogen mustard ICLs (23). Taken together these findings suggest that mismatch repair factors and Ercc1-Xpf are involved in a novel pathway of ICL repair.

A number of genetic screens have been undertaken in budding yeast to identify novel genes involved in ICL repair. One isolated mutant, psos4-1, exhibited some sensitivity to irradiation but was particularly sensitive to psoralen and other ICL-inducing agents (24, 25). It was also shown to be defective in some forms of recombination such as gene conversion, crossing over, and intrachromosomal recombination. Cloning of PSO4 showed that it was allelic to PRP19, an essential component of the pre-mRNA spliceosome in both yeast and human cells (25–30). Thus, PRP19/PSO4 appears to play dual roles in the cell; it has an essential function in pre-mRNA splicing and a role in the processing of DNA lesions particularly ICLs. Interestingly, human PSO4/PRP19 has also been isolated from human cell extracts as a component of the nuclear matrix and termed NMP200 (31). The human protein has also been shown to interact with terminal deoxynucleotidyltransferase and to be involved in mediating cell survival after DNA damage (32). Psos4/
**Pso4 and WRN in ICL Repair**

Psrp19 interacts with other components of the spliceosome and forms a highly stable core complex with a number of proteins including Cdc5L (Cef1 in *Saccharomyces cerevisiae*) (28, 33). WRN is a member of the RecQ family of DNA helicases and is mutated in the human autosomal recessive disease Werner syndrome (WS) (34). This disease manifests a number of phenotypes including generic instability, premature aging, and cancer predisposition (40). WRN possesses both a 3’ to 5’ helicase activity and a 5’ to 3’ exonuclease activity in different domains of the protein (35–40). WRN has been shown to have a role in mediating cell survival and functioning in homologous recombination in response to DNA damage (41–43). Consistent with these findings WS cells have been shown to be hypersensitive to a number of DNA damaging agents and are particularly sensitive to ICL-inducing compounds (43–45).

To investigate the mechanisms of ICL repair we have developed an *in vitro* assay in which repair processing in a plasmid substrate containing a site-specific psoralen cross-link can be monitored in mammalian cell extracts (18–21, 46). Using this assay, we report here the fractionation and identification of a protein complex composed of Pso4/Psrp19, Cdc5L, Plr1, and Spf27 (Pso4 complex) that is required for processing of psoralen ICLs *in vitro*. In addition, we show that the WRN protein is also absolutely essential to this processing and that WRN interacts with the Pso4 complex mediated by a direct association with Cdc5L.

**EXPERIMENTAL PROCEDURES**

**Cell Culture**—Human lymphoid cell lines were cultured in suspension in RPMI 1640 medium with 20% fetal calf serum. HeLa cells and HEK293 cells were cultured in DMEM containing 10% serum. Transfection of plasmids and siRNA were performed using FuGENE 6 and Oligofectamine (Invitrogen), respectively, following the manufacturer’s instructions. Cells were harvested 48 h after the transfection and prepared for co-immunoprecipitation or colonogenesis assays.

**EXPERIMENTAL PROCEDURES**

**Recombinant Proteins and Antibodies**—cDNAs for the Pso4 complex proteins were cloned into the Gateway cloning system (Invitrogen) for expression in *E. coli*, SF9 insect cells, or mammalian cells. The vectors expressing WRN proteins were generously provided by Judith Campisi. Recombinant 6xHis-Cdc5L, 6xHis-Plr1g, 6xHis-Pso4, 6xHis-Spf27, 6xHis-WRN, 6xHis-WRN(84A), and 6xHis-WRN(1–333) were expressed in SF9 insect cells using a baculovirus expression system. Proteins were purified by nickel affinity and Mono Q chromatography.

Polyclonal antibodies against Cdc5L, Plrg1, Pso4, and Spf27 were generously provided by Paul Ajuh (28). A monoclonal antibody against Cdc5L was purchased from BD Biosciences. Monoclonal antibodies against GST and GFP are from Santa Cruz Biotechnology. Polyclonal antibodies against GST and WRN are from Sigma, respectively.

**Fractionation of HeLa Nuclear Extract and in Vitro Interstrand Cross-link Repair (CRS) Assay**—HeLa nuclear extracts were prepared as described previously (20, 47). Nuclear extract was subjected to sequential chromatography using P11 phosphocellulose, hydroxyapatite, heparin-agarose, Mono S, and Mono Q. Active fractions were determined by reconstitution of the CRS assay with fractions FI and FII. The active fraction from the Mono Q column was used to elute 12% SDS-PAGE, protein bands were visualized by silver staining, and isolated bands were subjected to mass spectrometry analysis.

Psoralen interstrand cross-linked substrates for the CRS assay were prepared as described previously (18). Mammalian whole-cell extracts were prepared as described (48) and were tested for competency in a *in vitro* NER assay (49). The CRS assay was performed as described previously (18, 19). For reconstitution assays, 25 μg of HeLa nuclear extract, or 10 μg of fraction FI, 10 μg of fraction FII, and 2–4 μl of fraction FIII were used for each reaction.

**Immunodepletion, Co-immunoprecipitation, and Pull-down Assays**—Immunodepletion and coimmunoprecipitation assays were performed as described previously (50).

For pull-down assays GST-tagged proteins were bound on glutathione-Sepharose beads according to manufacturer’s instructions (Amersham Biosciences). The immobilized proteins were washed with Nonidet P-40 buffer (20 mM Tris, pH 8, 100 mM NaCl, 1 mM EDTA, 0.5% Nonidet P-40), then nuclear extract or purified proteins was added to the beads and incubated for 2 h at 4°C. The unbound proteins were removed by washing the beads four times with 100 bed volumes of Nonidet P-40 buffer. The bound proteins were eluted by boiling in SDS-PAGE sample buffer and visualized after gel electrophoresis by immunoblot analysis.

**Colonogenic Survival Assay**—Cdc5L and Pso4 were depleted by transfection of HeLa cells with siRNAs. The siRNA sequences used to knockdown Cdc5L and Pso4 were GGAAAGAGAGGUUGAUUA and ACCACAGGCUUGCUCUAAU, respectively. Forty-eight hours after transfection, cells were trypsinized and plated at the indicated density. Twelve to 15 days later, colonies were fixed and stained with crystal violet (0.25% crystal violet, 0.2% paraformaldehyde, 72% methanol, 18% water) and counted.

**Reactivation Assay**—Substrate preparation and the luciferase-based reactivation were performed as described previously (15).

**RESULTS**

The Pso4 Complex Is Required for In Vitro Processing of ICLs—To elucidate the processing of ICLs in mammalian cells, we have developed an *in vitro* assay (referred to as CRS) in which a single psoralen ICL located at a defined site within a plasmid substrate induces DNA synthesis in both damaged and undamaged plasmids in cell-free extracts (18). The substrates for this assay are described in the legend to Fig. 1A. The donor template plasmid is added to the reactions primarily as a carrier to absorb nonspecific inhibitory DNA binding proteins. As shown previously (19), the products of the *in vitro* processing of psoralen ICLs are two oligonucleotides migrating at the positions of 113 and 86 nucleotides on denaturing gels, which are derived from uncoupling of the ICL (supplemental Fig. S1). To identify additional factors involved in the processing of ICLs, we have initiated fractionation of HeLa nuclear extracts. P11 phosphocellulose column chromatography of HeLa nuclear extracts yielded four fractions, FI, FII, FIII, and FIV. All four of these proteins have been shown previously to be core components of a human Cdc5L-containing sub-pre-mRNA spliceo-
FIGURE 1. CRS assay and purification of the Pso4 complex. A, substrates for CRS assay. CLT, cross-linked template; DT, donor template. "X" indicates the site of psoralen interstrand cross-link in the cross-linked template. B, fractionation of HeLa cell extracts by P11 phosphocellulose column chromatography. Indicated proteins are required for full activity in the CRS assay. Fraction FIII was further fractionated by heparin, hydroxyapatite, Mono S, and Mono Q chromatography. Results of CRS assays from the final two columns are shown. All reactions contained phosphocellulose fractions FI and FII. Asterisks indicate active fractions that were used for further purification or analysis by mass spectroscopy. C, denaturing PAGE shows results of analysis of chromatography fractions in the CRS assay. The bands migrating at 113 and 86 nucleotides are diagnostic for the CRS assay. D, silver stain and Western blot analysis of fractions from the Mono Q column and identification of indicated bands by mass spectroscopy. Asterisks indicate the active fraction that was processed for mass spectroscopy. † indicates bands that were identified as degradation products of Cdc5L.
some complex that is conserved from yeast to mammals (28, 30, 51–53). Interestingly, the only known catalytic domain in any of the four proteins is an ubiquitin E3 ligase located in the U-box domain of Pso4/Prp19 (54–56). In addition, two of the proteins, Pso4 and Plrg1, contain WD40 domains, all of which suggests that these proteins may play a largely structural role. For convenience, we will here designate these four proteins as the Pso4 complex.

To verify the role of the Pso4 complex in ICL processing, we first immunodepleted Cdc5L from HeLa extracts (Fig. 2A) and then examined the activity of these depleted extracts in the CRS assay. As shown (Fig. 2B), depletion of Cdc5L resulted in a substantial reduction in the CRS assay. Furthermore, addition of purified recombinant Pso4 complex prepared from baculovirus (shown in Fig. 2C) was able to rescue the Cdc5L-depleted extracts. Next we examined various combinations of the recombinant Pso4 complex in the CRS assay. As shown (Fig. 2C, left panel), none of the individual proteins could substitute for FIII; however, addition of all four proteins did result in complementation approximately equivalent to that observed upon addition of FIII. In addition, no combination of any three of the proteins was able to effect complementation in the assay (Fig. 2C, right panel). Thus, we conclude that all four proteins are required for processing of psoralen ICLs in vitro and that the Pso4 complex is sufficient to substitute for fraction FIII in the CRS assay.

**PsO4 and Cdc5L Are Involved in Repair of ICLs in Vivo**—To determine whether PsO4/Prp19 or Cdc5L is involved in mediating resistance to ICL-inducing agents in vivo, we used siRNA to deplete these proteins in HeLa cells. However, in contrast to a previous report (32) we found that transfection of duplex siRNA oligonucleotides targeting either PsO4 or Cdc5L was growth inhibitory for HeLa cells (supplemental Fig. S2), thus precluding cell survival studies after exposure to genotoxic agents. The reason for this discrepancy is not clear, but both of these factors are essential in yeast cells due to their role in pre-mRNA splicing, and this role appears to be conserved in mammalian cells (28, 57, 58).

We have shown in recent studies that wild-type mammalian cells are able to repair cross-linked plasmids upon transfection as determined by a luciferase reactivation assay (14, 15). We therefore used this short term assay after knockdown of PsO4 or Cdc5L by siRNA to examine the role of these factors in ICL repair in vivo. As shown (Fig. 3), depletion of either PsO4 or Cdc5L showed a substantial and highly reproducible reduction in the reactivation of psoralen cross-linked plasmids. These results were not due to differences in cellular transfection efficiency, since a GFP-expressing plasmid was included in each experiment to allow for normalization of the luciferase reactivation.

**The PsO4 Complex Associates with the Werner Syndrome Protein through a Direct Interaction with Cdc5L**—To determine whether the PsO4 complex interacted with the previously identified components of ICL processing, we performed co-immunoprecipitation experiments. Antibodies to either Cdc5L or PsO4 were used for immunoprecipitation, and blots were subsequently analyzed for the presence of the previously identified components of the Pso4 complex. As shown (Fig. 4A), antibodies co-immunoprecipitated Cdc5L from HeLa nuclear extracts, and this role appears to be conserved in mammalian cells (28, 57, 58).

**The Pso4 Complex Interacts with the Werner Syndrome Protein through a Direct Interaction with Cdc5L**—To determine whether the PsO4 complex interacted with the previously identified components of ICL processing, we performed co-immunoprecipitation experiments. Antibodies to either Cdc5L or PsO4 were used for immunoprecipitation, and blots were subsequently analyzed for the presence of the previously identified components of the Pso4 complex. As shown (Fig. 4A), antibodies co-immunoprecipitated Cdc5L from HeLa nuclear extracts, and this role appears to be conserved in mammalian cells (28, 57, 58).
interacted directly with WRN, co-immunoprecipitation experiments were performed with purified recombinant proteins. As shown (Fig. 4B, upper blot), only Cdc5L showed a strong interaction with WRN. As a control, the ability of the indicated antibodies to co-immunoprecipitate was demonstrated by immunoblotting for Cdc5L after immunoprecipitation from nuclear extracts (Fig. 4B, lower blot).

To further assess this physical association, we mapped the sites of interaction between Cdc5L and WRN using GST-mediated pull-down assays with recombinant proteins. The WRN interaction site in Cdc5L was located between amino acid residues 74–300 (Fig. 5, A and B) indicating that it maps downstream of the Myb-like DNA binding domains. A strong interaction with Cdc5L was mapped between WRN amino acid residues 315–964, which encompasses the DNA helicase domain but which excludes the exonuclease domain (Fig. 5, C and D). A weak interaction was observed with a WRN fragment containing residues 1–640, which is truncated in the middle of the helicase domain, which further suggests that the interaction with Cdc5L occurs in this domain. Because of this latter finding, we examined whether the Pso4 complex stimulates the DNA helicase activity of WRN on a forked substrate (60); however, no stimulation of this activity was observed (Fig. S3).

The Werner Syndrome Protein Is Required for in Vitro Processing of Psoralen ICLs—As described above, WRN interacts with the Pso4 complex, and others (43–45) have shown that WS cells are hypersensitive to the introduction of ICLs. We therefore examined whether WRN was involved in the CRS assay. As an initial approach, we performed the CRS assay in the presence of a specific inhibitor (tetra-N-methylpyridylporphin) of RecQ helicases (61) and found that this drug was strongly inhibitory (Fig. 6A). We then used immunodepletion to remove WRN from HeLa nuclear extracts. While the immunodepletion was not quantitative, reduction of WRN in the extract corresponded well with a diminution of activity in the CRS assay (Fig. 6B, compare lanes 4 and 5).

Next we prepared whole cell extract from a WS cell line (AG04103) and found that this extract showed no detectable activity in the CRS assay (Fig. 6C). However, recombinant WRN proteins including wild-type and an E84A mutation, which abrogates the exonuclease activity (38), were able to complement the WRN-deficient extract, while an amino terminus fragment containing the exonuclease domain did not complement. Taken together, these findings indicate that WRN is required in the initial stages of processing of psoralen ICLs in vitro and that the DNA helicase, but not the exonuclease function, is a necessary component of this activity. Finally, Western blot analysis of phosphocellulose fractions FI, FII, and FIII indicated that WRN was contained in fraction FII.

DISCUSSION

Using biochemical fractionation and our previously established in vitro assay, we have identified a four-protein complex composed of Pso4/Prp19, Cdc5L, Plrg1, and Spf27 that is required for processing of psoralen ICLs. In addition, we also show that Pso4 and Cdc5L are required for full reactivation of psoralen cross-linked plasmids in vivo. Previous studies have shown that the Pso4 complex has a defined and conserved role in pre-mRNA splicing (25–29, 62, 63) and has been...
implicated in the repair of damaged DNA in both yeast and mammalian cells (24, 25, 32). Furthermore, at least one member of this complex, Pso4/Prp19, has been shown in mammalian cells to fractionate with the nuclear matrix (31). In particular, this latter observation may suggest a plausible mechanism by which the Pso4 complex might participate in both pre-mRNA splicing reactions and DNA damage processing. Numerous studies have implicated an involvement of the nuclear matrix in the nuclear metabolic processes of replication, transcription, RNA splicing, and DNA damage processing. With regard to DNA repair, experiments conducted in the 1980s clearly established that genomic DNA associated with the nuclear matrix or scaffold was preferentially repaired after UV treatment (66). More recent studies have shown that damaged DNA is recruited to the nuclear matrix after exposure to UV or UV mimetic compounds suggesting that “repair factories” are associated with the nuclear matrix (67, 68). Biochemical studies have revealed a more direct interaction between repair proteins and nuclear matrix components. As examples, the nuclear matrix protein C1D interacts with and stimulates the activity of the DNA-dependent protein kinase during repair of double-strand breaks by the nonhomologous end-joining pathway (69, 70). In addition, DNA-dependent protein kinase bound to DNA ends was shown to preferentially interact with plasmid DNA containing matrix attachment regions (71). Matrix attachment regions are specialized DNA sequences that anchor chromosomal loop attachment sites to the nuclear matrix (64). The Cockayne syndrome group A protein rapidly translocates to the nuclear matrix after UV irradiation where it co-localizes with RNA.

FIGURE 5. Mapping of the domains that mediate the interaction between WRN and Cdc5L. A, Western blot showing recombinant wild-type and truncated forms of Cdc5L fused to GST (left panel). Western blot showing pull-down assays conducted with recombinant WRN and GST-Cdc5L proteins (right panel). B, schematic illustration showing Cdc5L deletion mutants and the results of their interaction with WRN as determined by pull-down assays shown in A. C, Coomassie Blue-stained gel showing recombinant GST-WRN proteins (left panel). Western blot showing pull-down assays conducted with recombinant Cdc5L and GST-WRN proteins (right panel). D, schematic illustration showing WRN deletion mutants and the results of their interaction with Cdc5L as determined by pull-down assays shown in C. The schematic of WRN was adopted from von Kobbe et al. (59).
Polymerase II (72). The Fanconi anemia group D2 protein interacts with the nuclear matrix protein menin, and this interaction is enhanced by \( \gamma \) irradiation (73). Furthermore, loss of menin results in greater cellular sensitivity to DNA damage. Finally, both the Bloom syndrome protein (BLM) and WRN, members of the RecQ helicase family, have been shown to co-localize to and co-purify with the nuclear matrix (59, 74). Taken together, these findings and others clearly indicate a role for the nuclear matrix in DNA repair processing. Our findings extend these studies by demonstrating a direct role for the Pso4 complex in the processing of psoralen ICLs. While the nature of this role remains incompletely defined, a plausible scenario is that the complex acts as a scaffold for the recruitment of other repair factors. Previously, Pso4/Prp19 has been shown to co-immunoprecipitate with terminal deoxynucleotidyl transferase (32), and we have shown here that the complex associates with WRN through a direct interaction with Cdc5L.

WRN has been shown to interact with a large number of proteins involved in DNA repair and has been implicated in several DNA repair pathways including repair of double-strand breaks, base excision repair, and repair of ICLs, but its precise role in these pathways has remained somewhat elusive (75, 76). Our findings demonstrate that WRN is an
essential factor in the processing of psoralen ICLs \textit{in vitro} and that its DNA helicase, but not its exonuclease activity, is a required function in this process. Parenthetically, the WS cell line (AG04103) used for extract preparation contains a homozygous mutation that truncates WRN upstream of the helicase domain. Additionally, our preliminary mapping of the Cdc5L interaction domain indicates that it lies within the helicase domain of WRN. Despite this finding we did not observe stimulation of the WRN helicase activity by the Psq4 complex on a forked substrate, although it is conceivable that this could occur on a cross-linked substrate. Interestingly, all of the previously identified 14 functionally significant protein interactions with WRN have been mapped downstream of the helicase domain in the RQC region (76).

We previously proposed a model for processing of ICLs that postulated that a DNA helicase would be required to form an open or bubble structure downstream of the adduct, which would allow uncoupling of the ICL by the Ercc1-Xpf endonuclease (20). An updated model illustrating how ICL processing might be accomplished \textit{in vivo} with the factors identified by our biochemical studies is shown in Fig. 7. The salient features of this model are recognition of the ICL by MutSβ with stimulation by PCNA (19), recruitment of the Psq4 complex, WRN, and RPA to the site by an unknown mechanism, and recruitment of the Ercc1-Xpf endonuclease, which results in uncoupling of the ICL. This latter concept is based on findings showing that Ercc1-Xpf can incise on either side of a psoralen ICL when it is located near the junction of duplex and single-stranded DNA (77). Furthermore, Ercc1-Xpf has been shown to associate with Msh2 (22) and thus may be recruited to the lesion through an interaction with MutSβ. Finally, it should be mentioned that attempts to reconstitute the uncoupling reaction with the components shown in Fig. 7 have not been successful indicating that additional components of this pathway remain to be identified.

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**FIGURE 7.** Model depicting repair of ICLs. \(a\), the binding of MutSβ to an ICL is stimulated by PCNA. \(b\), the WRN helicase in cooperation with RPA and the Psq4 complex creates a bubble or open region proximate to the ICL. \(c\), Ercc1-Xpf is recruited to the site presumably by interaction with MutSβ and forms incisions on either side of the lesion creating a single-stranded gap (\(d\)). \(e\), the resulting gap is repaired by either translesion bypass synthesis or homologous recombination.
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