Human Xip1 (C2orf13) Is a Novel Regulator of Cellular Responses to DNA Strand Breaks

Received for publication, March 30, 2007, and in revised form, May 3, 2007. Published, JBC Papers in Press, May 16, 2007, DOI 10.1074/jbc.C700060200

Simon Bekker-Jensen, Kasper Fugger, Jannie Røndtlev Danielsen, Irina Gromova, Maxwell Sehested, Julio Celis, Jiri Bartek, Jiri Lukas, and Niels Mailand

From the 4Centre for Genotoxic Stress Research and the 5Department of Proteomics in Cancer, Institute of Cancer Biology, Danish Cancer Society, Copenhagen DK-2100 and the 6Department of Pathology, University Hospital, DK-2100 Copenhagen, Denmark

DNA strand breaks arise continuously as the result of intraacellular metabolism and in response to a multitude of genotoxic agents. To overcome such challenges to genomic stability, cells have evolved genome surveillance pathways that detect and repair damaged DNA in a coordinated fashion. Here we identify the previously uncharacterized human protein Xip1 (C2orf13) as a novel component of the checkpoint response to DNA strand breaks. Green fluorescent protein-tagged Xip1 was rapidly recruited to sites of DNA breaks, and this accumulation was dependent on a novel type of zinc finger motif located in the C terminus of Xip1. The initial recruitment kinetics of Xip1 closely paralleled that of XRCC1, a central organizer of single strand break (SSB) repair, and its accumulation was both delayed and sustained when the detection of SSBs was abrogated by inhibition of PARP-1. Xip1 and XRCC1 stably interacted through recognition of CK2 phosphorylation sites in XRCC1 by the Forkhead-associated (FHA) domain of Xip1, and XRCC1 was required to maintain steady-state levels of Xip1. Moreover, Xip1 was phosphorylated on Ser-116 by ataxia telangiectasia-mutated in response to ionizing radiation, further underscoring the potential importance of Xip1 in the DNA damage response. Finally, depletion of Xip1 significantly decreased the clonogenic potential of cells exposed to DNA SSB- or double strand break-inducing agents. Collectively, these findings implicate Xip1 as a new regulator of genome maintenance pathways, which may function to organize DNA strand break repair complexes at sites of DNA damage.

The DNA damage response is a complex and multifunctional network of pathways collectively acting to maintain genomic stability of all living organisms. This machinery is activated in response to a multitude of genotoxic insults, impacting on and coordinating a diverse range of cellular processes such as cell cycle progression, DNA repair, DNA replication, and gene transcription (1). Several repair pathways exist to deal with the different types of DNA damage that can arise (2). One of these is the DNA SSB repair pathway, which deals with genuine DNA SSBs (the most frequent type of lesion in DNA) as well as the various base modifications that can be converted into SSBs by base excision repair enzymes.

The initial sensor of SSBs appears to be poly(ADP-ribose) polymerase-1 (PARP-1), which is rapidly recruited to and activated by SSBs (3, 4). The activity of PARP-1, in turn, is thought to modify and locally relax chromatin, allowing efficient access of DNA repair enzymes to SSBs. A number of DNA end-processing enzymes can act on crude lesions to convert the DNA ends into a common intermediate in order for gap filling and religation to occur. These enzymes include PNK, APE1, DNA pol β (5), and the recently identified disease-associated enzymes TDP1 and aprataxin (APTX) (6). The processed DNA ends are then rejoined by short-patch repair (for a single missing nucleotide) or long-patch repair (several nucleotides) (2, 5).

The protein XRCC1 is intimately involved in the repair of SSBs but is distinguishable from other SSB repair proteins by its lack of an enzymatic activity. Instead, it appears to act as a scaffold protein, interacting with (and in some cases activating) a range of SSB repair proteins (7). In this way, XRCC1 may organize SSB repair enzymes into a larger holocomplex with multifunctional roles in the repair of SSBs and oxidative DNA lesions. XRCC1 contains two BRCA1 C-terminal domains and has been shown to interact with PARP-1, pol β, and DNA ligase 3 among others (5, 8, 9). In addition, the linker region between the BRCA1 C-terminal domains in XRCC1 contains eight CK2 phosphorylation sites, which together constitute a binding platform for the FHA domains of PNK (10) and APTX (11, 12), and this interaction was shown to be responsible for the stable accumulation of PNK at sites of oxidative DNA damage (10).

In this report, we describe a potential involvement in DNA repair pathways of the previously uncharacterized human open reading frame C2orf13, which accumulates at sites of DNA damage via tandem zinc finger (ZnF) motifs and associates with XRCC1 by a mechanism analogous to those of PNK and APTX. Based on these and other findings, we denote this protein Xip1

1 To whom correspondence should be addressed: Centre for Genotoxic Stress Research, Institute of Cancer Biology, Danish Cancer Society, Strandboulevard 49, DK-2100 Copenhagen, Denmark. Tel.: 45-35-25-73-10; Fax: 45-35-25-77-21; E-mail: jil@cancer.dk

2 The abbreviations used are: SSB, single strand break; DSB, double strand break; ZnF, zinc finger; IR, ionizing radiation; ATM, ataxia telangiectasia-mutated; ATR, ATM and Rad3-related; pol, polymerase; PNK, polynucleotide kinase; APTX, aprataxin; GFP, green fluorescent protein; siRNA, small interfering RNA; WT, wild type; Gy, gray; FHA, forhead associated.

9 This work was supported by grants from the Danish Cancer Society, Danish National Research Foundation, Danish Research Council, European Union (integrated project “DNA Repair”), European Science Foundation (EuroDyna), SSMF Stockholm, and John and Birthe Meyer Foundation. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

10 The on-line version of this article (available at http://www.jbc.org) contains two supplemental figures.

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(XRCC1-interacting protein 1) and propose that it is a novel regulator of DNA strand break repair.

EXPERIMENTAL PROCEDURES

Plasmids—An IMAGE clone containing the full open reading frame of human Xip1 was obtained from RZPD, Berlin, Germany. To generate expression vectors for GFP- and Myc-tagged Xip1, this cDNA was amplified by PCR and inserted into pEGFP-N1 (Clontech) and pcDNA3 (Invitrogen) containing an N-terminal Myc tag, respectively. The *FHA (R27A), *ZnF-1 (C387A), *ZnF-2 (C427A), and candidate ATM phosphorylation site mutations were introduced using the QuikChange site-directed mutagenesis kit (Stratagene) (* denotes loss-of-function mutations). An expression plasmid for GFP-XRCC1 was generated by amplification of XRCC1 cDNA (a gift from Dr. K. Caldecott) by PCR and inserting it into pEGFP-C1 (Clontech). All plasmid transfections were performed using FuGENE 6 (Roche Applied Science).

RNA Interference—siRNA oligonucleotides (Dharmacon) were synthesized to the following sequences (sense strand): Xip1 (5'-UUCCCGAUUCUCCUAUA-3'), XRCC1 (5'-GACCAUCUGUGGUCUA-3'), and GL2 (control). ATM siRNA has been described previously (14). All siRNA transfections were performed with 100 nM siRNA duplexes using Lipofectamine RNAiMAX (Invitrogen).

Cell Culture—Human U-2-OS osteosarcoma cells were grown in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum (Invitrogen). U-2-OS cell lines stably expressing Xip1-GFP and GFP-XRCC1 were generated and maintained as described (15). To produce U-2-OS sublines stably expressing Myc-Xip1 (wild type (WT) and S116A), pcDNA3-Myc-Xip1 constructs were co-transfected with a puromycin resistance plasmid, and puromycin-resistant colonies were isolated and screened for homogenous expression of the transgenes. IR was delivered by an x-ray generator (Pantak HF160, 150 kV, 15 mA, dose rate 2.18 Gy/min). PARP-1 inhibitor (PJ34, Calbiochem) was used at a final concentration of 1 μM.

Immunoochemical Methods—Immunoprecipitation, immunoblotting, and immunofluorescence assays were described (13). Mouse antibody to Xip1 was raised against purified full-length, GST-tagged human Xip1. Other antibodies used in this study were mouse monoclonals to XRCC1 (Ab-1, NeoMarkers), ATM (MAT3, gift of Dr. Y. Shiloh), and Myc tag (sc-40, Santa Cruz Biotechnology), and rabbit polyclonals to XRCC1 (Ab-9147) and SMC1 (Ab-9262), both from AbCam.

Microscopy and Laser Micro-irradiation—Confocal images were acquired on LSM-510 (Carl Zeiss Microimaging Inc.) mounted on Zeiss-Axiovert 100 M equipped with Plan-Neofluor ×40/1.3 oil immersion objective. Laser micro-irradiation to generate DNA strand breaks in defined nuclear volumes, and conditions for time-lapse microscopy were as described (16, 17).

Gel Filtration—Total cell extracts were prepared as described (13), separated on the ÄKTA Explorer gel filtration system (Amersham Biosciences) using Superose 6 columns (Amersham Biosciences), and collected in 0.3-ml fractions. Proteins were precipitated by incubation with acetone at −20 °C for 12 h and centrifuged at 20,000 rpm for 10 min, and the pellet was resuspended in Laemmli sample buffer and resolved on SDS-PAGE.

Clonogenic Survival Assays—U-2-OS cells were transfected with control or Xip1 siRNAs. Three days after transfection, cells were replated and left to adhere for 12 h and then subjected to IR or treated with camptothecin for 24 h. Subsequently, cells were incubated for an additional 14 days and stained with crystal violet. Colonies containing more than 50 cells were counted.

RESULTS

Xip1 Rapidly Accumulates at Sites of DNA Damage—We screened a panel of uncharacterized human proteins harboring domains commonly found in known regulators of the DNA damage response for their possible involvement in this response. One of these proteins, C2orf13, appeared as an attractive candidate as it contains an N-terminal FHA domain (found in a range of proteins involved in the response to DNA damage (18)) as well as potential ZnF and coiled coil motifs in the C terminus (Fig. 1A). For reasons described below, we named this uncharacterized protein Xip1 (XRCC1-interacting protein 1).

To assess whether Xip1 was indeed involved in the response to DNA damage, we generated a U-2-OS cell line stably expressing GFP-tagged Xip1 and assayed its behavior following exposure to genotoxic stimuli. Xip1-GFP localized to the nucleus throughout interphase in undamaged cells and accumulated both at IR-induced nuclear foci and in micro-laser-generated tracks (Fig. 1B). Notably, the recruitment of Xip1-GFP was exceedingly rapid, reaching a peak immediately after the infliction of DNA damage (Fig. 1, C (upper panels) and D). This accumulation was transient, too, as the bulk of recruited Xip1-GFP was lost from the sites of damage within 10 min (Fig. 1, C and D). This behavior sets Xip1 apart from proximal DNA double strand break (DSB) regulators, which accumulate at DSBs in a more gradual fashion and remain bound for an extended period at the irradiation doses used in this study (15, 16). On the other hand, the rapid kinetics of Xip1-GFP recruitment to sites of DNA damage closely paralleled that of GFP-tagged XRCC1 (Fig. 1, C (lower panels) and D), suggesting that Xip1 might be a novel component of the response to DNA SSBs. Like Xip1, XRCC1 accumulated only transiently at DNA lesions but was retained somewhat longer than Xip1 (Fig. 1, C and D), suggesting that XRCC1 performs a broader role at the sites of DNA repair, whereas Xip1 is primarily important for the immediate response to the DNA insult. Interestingly, the recruitment of Xip1-GFP to DNA lesions was significantly delayed and sustained in the presence of an inhibitor of PARP-1 (Fig. 1E), the key initiator protein of SSB repair, further underscoring a potential role of Xip1 in this process.

Xip1 Is Recruited to Sites of DNA Damage through a Novel, Tandem ZnF Motif—Having shown that Xip1 rapidly accumulates at sites of damaged DNA, we next sought to identify the structural motif(s) in Xip1 mediating this interaction. A deletion analysis pinpointed the potential tandem ZnFs in Xip1 as the domain responsible for its recruitment (data not shown). This motif strongly resembles a novel type of C2H2
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zinc finger motif (with a $C_{X_5}C_{X_4}H_{X_5}H$ configuration), and a BLAST analysis revealed that this motif is present in a number of proteins through evolution, all of which appear to have roles in DNA binding or DNA metabolism. Only in Xip1, however, is this motif present in tandem, and it is highly conserved in putative Xip1 orthologues across eukaryotes (supplemental Fig. S1). To clarify whether the tandem zinc finger motifs were responsible for recruiting Xip1 to sites of DNA damage, we substituted the second conserved cysteine in either or both of the C5C4H5H clusters completely abrogated Xip1 binding to sites of DNA damage as in Fig. 2A. *FHA, *ZnF-1, *ZnF-2, and ATM phosphorylation site mutants are indicated. B, U-2-OS/Xip1-GFP cells were left untreated or subjected to IR (4 Gy) or micro-laser irradiation and subjected to time-lapse microscopy immediately after treatment. Mock, mock-transfected. C, U-2-OS/Xip1-GFP or U-2-OS/GFP XRCC1 cells were micro-laser-irradiated and photographed at various times after treatment as in B. D, quantification of the experiment shown in Fig. 1C. NFU, normalized fluorescence units. E, U-2-OS/Xip1-GFP cells were treated with PARP-1 inhibitor for 1 h and then subjected to micro-laser irradiation and processed as in C.

**Xip1 Interacts with XRCC1**—To gain insight into the function of Xip1 in the DNA damage response, we set out to identify Xip1-interacting proteins. The rapid and comparable recruitment kinetics of Xip1 and XRCC1 in response to micro-laser irradiation prompted us to assess whether the two proteins formed a complex. To test this idea, we used a mouse antibody raised against human Xip1 to immunoprecipitate endogenous Xip1 protein from total cell extracts. As shown in Fig. 2B, XRCC1 was specifically detected in Xip1 immunocomplexes but not in immunoprecipitates of a preimmune serum, suggesting that Xip1 and XRCC1 are indeed found in a common complex. This association was not significantly affected by DNA-damaging agents (data not shown). Next we asked whether the Xip1-XRCC1 interaction was mediated by the FHA domain of Xip1. Wild-type Myc-tagged Xip1 or a point mutation abolishing the functionality of its FHA domain (Fig. 1A, *FHA) was transfected into U-2-OS cells and assessed for its ability to co-immunoprecipitate endogenous XRCC1. In agreement with the results in Fig. 2B, we observed a robust interaction between WT Myc-Xip1 and XRCC1 (Fig. 2C). In contrast, introduction of the FHA mutation into Xip1 fully abrogated this interaction, demonstrating that Xip1 recognizes XRCC1 through its FHA domain. Since FHA domains bind target
proteins in a phosphorylation-dependent manner (19, 20) and the FHA domain-dependent bindings of PNK and APTX to XRCC1 have both been shown to involve the recognition of CK2 phosphorylation sites in XRCC1 (10, 12), we asked whether Xip1 would associate with XRCC1 in a similar fashion. To this end, we tested the ability of WT or a CK2 phosphorylation-deficient mutant of XRCC1 (XRCC1-CKM (10)) to interact with Myc-Xip1. This analysis clearly showed that XRCC1-CKM was completely unable to bind Xip1 (Fig. 2D), demonstrating that Xip1 binding to XRCC1 involves its FHA domain-dependent recognition of CK2 phosphorylation sites in XRCC1. Thus, the association of XRCC1 with Xip1, PNK, and APTX appears to be mediated by similar mechanisms.

To further probe the nature of the interaction between Xip1 and XRCC1, we depleted either protein by siRNAs and tested the impact of such treatment on its binding partner. Strikingly, although depletion of Xip1 did not have a significant impact on XRCC1 expression, the knockdown of XRCC1 led to a strong reduction in the protein level of Xip1 (Fig. 2E). Thus, the interaction between XRCC1 and Xip1 appears to be required to maintain the steady-state level of endogenous Xip1; a similar increase in stability was previously observed for DNA ligase 3 upon binding to XRCC1 (21). Moreover, gel filtration analysis showed that the distribution patterns of Xip1 and XRCC1 in the eluted fractions were strikingly similar (Fig. 2F), suggesting that the majority of Xip1 protein is associated with XRCC1. This is in agreement with the notion that the binding of Xip1 to XRCC1 is dependent on phosphorylation of XRCC1 by the constitutively active CK2 kinase(s) and that the stability of Xip1 is dependent on the presence of XRCC1.

We wished to determine whether Xip1 was required for the recruitment of XRCC1 to sites of DNA repair and vice versa. For this purpose, we monitored the propensity of GFP-tagged Xip1 or XRCC1 to accumulate at damaged DNA after siRNA-mediated depletion of the other component. As shown in supplemental Fig. S2, neither the recruitment of Xip1-GFP nor the recruitment of GFP-XRCC1 was markedly impaired by the loss of the other component, indicating that despite their avid interaction, Xip1 and XRCC1 can be targeted to DNA lesions independently of each other.

**Xip1 Is Phosphorylated by ATM on Serine 116 in Response to IR**—To further establish Xip1 as a component of the DNA damage response, we tested whether it was modified by ATM/ATR-mediated phosphorylation in response to DNA damage. Cells were subjected to various DNA-damaging stimuli and probed for the electrophoretic mobility of Xip1 on SDS-PAGE. As shown in Fig. 3A, endogenous Xip1 underwent a prominent mobility shift in response to IR but was not detectably modified following exposure to UV or hydroxyurea, suggesting that Xip1 is phosphorylated by ATM in response to DSBs, whereas it does not appear to be a target for ATR. Treatment with a phosphatase completely prevented the IR-induced mobility shift of Xip1 (Fig. 3B), demonstrating that it was indeed due to phosphorylation. To confirm that the phosphorylation of Xip1 was dependent on ATM, we evaluated the IR-dependent mobility shift of Xip1 in cells depleted of ATM by siRNAs. Such treatment largely prevented the IR-induced modification of Xip1, indicating that Xip1 is phosphorylated in an ATM-dependent manner in response to IR (Fig. 3C).

We attempted to identify the major ATM phosphorylation site(s) in Xip1 and embarked on an alanine substitution strategy, mutating individual SQ/TQ-sites (seven of which are present in human Xip1) and probing such mutants for their IR-dependent mobility shift. Interestingly, a single S116A substitution rendered Myc-Xip1 less susceptible to ATM-mediated phosphorylation as judged by the virtually complete lack of mobility shift of this mutant (Fig. 3D), whereas mutation of none of the other potential ATM phosphorylation sites significantly affected the ability of Myc-Xip1 to shift on SDS-PAGE in response to IR (data not shown). Thus, S116, which is highly conserved among mammalian species, appears to be the major ATM phosphorylation site in Xip1, further demonstrating that Xip1 is phosphorylated by ATM in response to DNA strand breaks.

**Depletion of Xip1 Sensitizes Cells to DNA-damaging Agents**—The emerging role of Xip1 in the DNA damage response led us to assess its relative importance in this process. Cells transfected with control or Xip1 siRNAs were exposed to various DNA-damaging agents, and their sensitivity to the genotoxic insult was evaluated by conventional clonogenic survival assays. Consistent with a function in SSB repair, the depletion of Xip1 significantly reduced survival in response to camptothecin (CPT).

![FIGURE 3. Xip1 is phosphorylated by ATM on Ser-116 in response to IR and facilitates survival of cells exposed to DNA strand break-inducing agents. A, U-2-OS cells were left untreated (–) or subjected to IR (10 Gy), UV (20 J/m²), or hydroxyurea (HU) (5 mM), harvested 1 h later, and assayed for electrophoretic mobility shift of endogenous Xip1 by immunoblotting. B, U-2-OS/Myc-Xip1 cells were left untreated or exposed to IR (10 Gy) and harvested 1 h later. Anti-Myc immunoprecipitates from total cell extracts were mock-treated or incubated with λ phosphatase for 30 min and resolved by SDS-PAGE, and the mobility of Myc-Xip1 was determined by immunoblotting with Myc antibody. C, U-2-OS/Myc-Xip1 cells were transfected with control or ATM siRNAs for 72 h, exposed to IR (10 Gy), and processed as in A. D, 0.2-35S/Myc-Xip1 cells stably expressing either the WT or the S116A alleles were subjected to IR and processed as in A. E, clonogenic survival assays of U-2-OS cells transfected with control or Xip1 siRNAs and subjected to indicated doses of IR or camptothecin (CPT). The experiments were carried out in triplicates; error bars indicate the standard error.](https://example.com/figure3)
tothecin, a known inducer of SSBs (Fig. 3E). Notably, however, the survival rates of Xip1-depleted cells were comparably decreased in cells exposed to low doses of IR or methyl methanesulfonate (Fig. 3E and data not shown), indicating that Xip1 is required for the efficient repair of a broad range of DNA lesions.

**DISCUSSION**

In this study, we have identified the previously uncharacterized human protein Xip1 as a novel component of the DNA damage response. Mammalian Xip1 orthologues are highly conserved within their defined N- and C-terminal domains, and BLAST searches suggest that Xip1-like proteins are also present in a wider range of eukaryotes from flies to man, indicating that Xip1 plays an important, evolutionarily conserved role in the response to DNA damage.

A prominent feature of Xip1 presented here is its ability to rapidly and transiently accumulate at sites of damaged DNA, a behavior yielding important clues to its function in the DNA damage response. Although the kinetics of its recruitment did not parallel those of established DSB regulators, it closely resembled that of XRCC1, a central organizer of the SSB repair response, and was markedly modulated in response to inhibition of PARP-1, a key proximal detector of DNA SSBs. Together with the notion that Xip1 appears to form a stable complex with XRCC1, these data strongly support the idea that Xip1 is intimately involved in some aspect of SSB repair, consistent with the rapid nature of this process. We could demonstrate that Xip1 is recruited to damaged DNA through a novel tandem ZnF motif located in the C terminus of the protein. This likely reflects the direct recognition of damaged DNA by Xip1 since its accumulation at these sites does not appear to depend on XRCC1. Interestingly, a number of SSB repair proteins (including PARP-1 and DNA ligase 3) contain ZnF motifs that contribute to their recruitment to damaged DNA structures (5), and the data presented in this study indicate that Xip1 may accumulate at sites of chromosomal breakage in a similar fashion. The unusual (tandem) $\text{CX}_2\text{CX}_2\text{H}_x\text{H}$ configuration of the Xip1 ZnF motif might function to recognize a unique, as yet unknown, structure in DNA, brought about by exposure to DNA-damaging agents. The observation that Xip1 is only transiently maintained at sites of damaged DNA suggests that the particular type of lesion to which Xip1 binds is rapidly repaired, causing the subsequent dissociation of Xip1 from DNA. This idea is supported by our finding that Xip1-GFP exhibits prolonged retention at sites of DNA damage in response to PARP-1 inhibition, presumably because the structures recognized by the ZnFs of Xip1 are not repaired in a timely fashion.

Xip1 contains an N-terminal FHA domain, a motif frequently found in components of the DNA damage response (18), and we have shown that a key function of this domain is to mediate the interaction of Xip1 with XRCC1. This binding depends on the prior phosphorylation of the latter protein by CK2 kinases, which are constitutively active, agreeing well with the finding that Xip1 and XRCC1 form a complex even in undamaged cells. The CK2 requirement for Xip1 binding to XRCC1 is not unexpected as the FHA domain of Xip1 aligns well with those of PNK and APTX (data not shown), providing an explanatory basis for their common preference for CK2-phosphorylated XRCC1. As we have shown, an important aspect of the FHA domain-dependent binding of Xip1 to XRCC1 may be to support the stability of the former protein. However, it is clearly possible that Xip1 might also employ its FHA domain to interact with additional proteins. It remains to be seen whether Xip1, PNK, and APTX compete for XRCC1 binding or recognize non-overlapping CK2 sites in XRCC1.

What is the precise function of Xip1 in DNA repair? The lack of any obvious catalytic domains suggests that like XRCC1, Xip1 functions predominantly in the organization of repair complexes at the sites of damaged DNA, in agreement with its rapid and transient accumulation in this compartment. The observed FHA domain-dependent binding to XRCC1 suggests that one important function of Xip1 may be to recruit XRCC1 to DNA lesions. However, cells depleted for Xip1 were not markedly impaired in XRCC1 accumulation at sites of chromosomal breakage, which might reflect the possibility that XRCC1 recruitment is complex and may also involve its direct targeting to the lesions or might occur via its interactions with other SSB repair components including PNK, APTX, pol β, and DNA ligase 3. It is possible that Xip1 serves to recruit XRCC1 to a particular subset of DNA lesions, which might be uniquely recognized by its tandem ZnF motifs. This scenario would be consistent with the fact that IR and micro-laser irradiation generate a multitude of lesions in DNA, only a subset of which might require Xip1-dependent recruitment of XRCC1, for which reason they might not be easily appreciable by the light microscopy approaches employed here. Alternatively, Xip1 might recruit one or more additional factor(s) to XRCC1-containing complexes at sites of DNA repair. Further studies should be aimed at addressing these complex issues.

Although the behavior of Xip1 described in this study would be primarily consistent with a role in SSB repair, the function of Xip1 in DNA repair may not necessarily be restricted to this process. In particular, a potential role of Xip1 in the repair of DSBs is suggested by our finding that depletion of Xip1 negatively affects the survival of cells exposed to both SSB-inducing and DSB-inducing agents. Moreover, we have identified several proteins in addition to XRCC1 to which Xip1 binds, including the Ku70-Ku86 complex, which plays an essential role in the repair of DSBs. Such a broader role in DNA repair is also warranted by the observation that Xip1 is phosphorylated by ATM, a modification that is not required for Xip1 recruitment to sites of DNA damage (data not shown) and that persists far beyond the time at which Xip1 is released from this compartment. In addition, none of the established SSB repair proteins have been described to be ATM targets, further indicating that Xip1 may have additional functions in the DNA damage response.

In conclusion, our data uncover an emerging role of Xip1 in the orchestration of DNA strand break repair. A more detailed insight into its precise function in this process should contribute to understanding the molecular aspects of cellular defense mechanisms against genomic instability.

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3 S. Bekker-Jensen, I. Gromova, J. Lukas, and N. Mailland, unpublished data.
Acknowledgments—We thank Keith Caldecott and Yossi Shiloh for providing reagents.

Note Added in Proof—While our paper was under review, two groups independently reported C2orf13 as a novel regulator of DNA strand break repairs (Iles, N., Rulten, S., El-Khamisy, S. F., and Caldecott, K. W., (2007) Mol. Cell. Biol. 27, 3793–3803; Kanno, S., Kuzuoka, H., Sasa, S., Hong, Z., Lan, L., Nakajima, S., and Yasui, A. (2007) EMBO J. 26, 2094–2103).

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