9

Human CtIP and Its Homologs: Team Players in DSB Resection Games

Yasuhiro Tsutsui, Akihito Kawasaki and Hiroshi Iwasaki
Department of Life Science, School and Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology
Japan

1. Introduction

Double-strand breaks (DSBs) are among the most serious forms of DNA damage and thus must be efficiently repaired. In order for effective repair to take place, cells must employ the following steps: 1) recognition of the DSBs, 2) cell-cycle arrest via checkpoint activation, and 3) repair of the breaks. In the repair step, DSB ends are nucleolytically processed, which leads to the subsequent recruitment of appropriate repair proteins. Several proteins, including the Mre11 nuclease, are known to be involved in the processing of DSB ends. Additionally, recent studies have identified human CtIP and its orthologs as novel components required for DNA end processing among eukaryotes. This protein is involved not only in repair via homologous recombination (HR) but also in several important biological processes, such as transcriptional regulation and checkpoint control. Importantly, CtIP acts as a tumor suppressor in mammals. In this chapter, we will summarize the existing knowledge on this multi-functional molecule.

2. Identification of CtIP

2.1 DSB repair pathways

DSBs could lead to chromosomal aberrations, the disruption of genome integrity, and tumorigenesis in higher eukaryotes. DSBs are generated either by exogenous sources such as gamma-irradiation or by endogenous factors such as replication fork collapse. In addition, programmed DSBs are induced during meiosis at several loci, known as recombination hot spots. While such programmed DSBs are repaired by error-free HR, incidentally-generated DSBs are repaired by one of two major DNA repair pathways: HR or error-prone non-homologous end-joining (NHEJ), both of which are highly conserved from yeast to humans. NHEJ and HR function predominantly in cell cycle phases G_1 and S/G_2, respectively. DSBs are repaired using intact homologous sequences (sister-chromatids or homologs) as a template in HR, whereas in NHEJ, the broken ends are directly rejoined.

When DSBs occur, a protein complex called MRN(X) (see below for details) is recruited at the DSB ends and activates the DNA damage checkpoint. The Ku70-Ku80 heterodimer, involved in the NHEJ pathway, is also recruited. The ends are then nucleolytically processed by the MRN(X) complex in a process called "DNA end resection" or simply "resection", leading to the conversion of "dirty ends" to repairable "clean ends". Human

CtIP and its orthologs, together with the MRN(X) complex, play a critical role in this DNA end processing.

2.2 Several Y2H screenings with different 'baits' identified CtIP

Human CtIP was first identified by a yeast two-hybrid (Y2H) assay as one of the interacting proteins of CtBP (**C** **t**erminus-**b**inding **p**rotein), which is a transcriptional corepressor (Schaeper et al., 1998). CtBP binds to the C-terminal PLDLS motif of adenovirus E1A, resulting in anti-tumorigenic activity (Schaeper et al., 1995; Boyd et al., 1993). CtIP was also identified as RBBP8 in another Y2H screen in which the retinoblastoma (Rb) protein, a tumor suppressor with a protein-binding "pocket" domain, was applied as a bait (Fusco et al., 1998). CtIP/RBBP8 contains the LECEE sequence, known as an Rb-binding domain, which is required for interaction with Rb in a Y2H system (Fusco et al., 1998). CtIP was also found to associate with Rb-related protein p130 in a different Y2H screening (Meloni et al., 1999).

The breast and ovarian tumor suppressor BRCA1 has important functions in cell cycle checkpoint control and DNA repair. Two tandem BRCA1 C-terminal (BRCT) motifs are essential for the tumor suppression activity of BRCA1. The BRCT motifs of BRCA1 have also been shown to interact with CtIP both *in vivo* and *in vitro* (Li et al., 1999; Wong et al., 1998; Yu et al., 1998).

CtIP has also been isolated in two independent Y2H assays with Ikaros and LMO4 used as bait proteins (Koipally and Georgopoulos, 2002; Sum et al., 2002). Ikaros is a zinc finger protein that plays key roles in hemolymphoid development and homeostasis (Koipally and Georgopoulos, 2002). LMO4 belongs to the LIM-only (LMO) group of transcriptional regulators (Sum et al., 2002).

2.3 Identification of CtIP homologs

Sae2/Com1 was identified in the budding yeast *Saccharomyces cerevisiae* (Sc) from two independent genetic screens for mutants showing sporulation in the absence of Spo11 (McKee and Kleckner, 1997b; 1997a; Prinz et al., 1997). However, in ten years, no structurally or functionally similar Sae2/Com1 homologs have been reported in any organism other than *Saccharomyces*. In 2007, Russell and colleagues identified the *ctp1*$^{+}$ gene when investigating a subclass of cell-cycle-regulated genes in *Schizosaccharomyces pombe* (Sp) (Limbo et al., 2007). A database search revealed that SpCtp1 is homologous to proteins that have previously been characterized in several species such as ScSae2/Com1, COM-1 in *Caenorhabditis elegans* (Ce), GR1 from *Arabidopsis thaliana* (At), and human CtIP (Limbo et al., 2007) (Fig. 1A).

SpCtp1 was also found to be coded by an *slr* (synthetically lethal with *rad2*Δ) gene and interacts genetically with the Nbs1 protein. Thus, it was originally termed as Nip1 (Nbs1 interacting protein 1) (Akamatsu et al., 2008).

CeCom-1 was originally identified from a mutagenesis screen for mutants causing maternal-effect embryonic lethality (Penkner et al., 2007; Gönczy et al., 1999). AtGR1 was isolated from a screen for mRNAs that accumulate after DNA damage induced by ionizing radiation (Deveaux et al., 2000).

2.4 CtIP is conserved protein from yeast to humans

As previously mentioned, *S. cerevisiae* Sae2/Com1 was first identified as a CtIP homolog (McKee and Kleckner, 1997b; 1997a; Prinz et al., 1997), but clear Sae2/Com1 homologs have

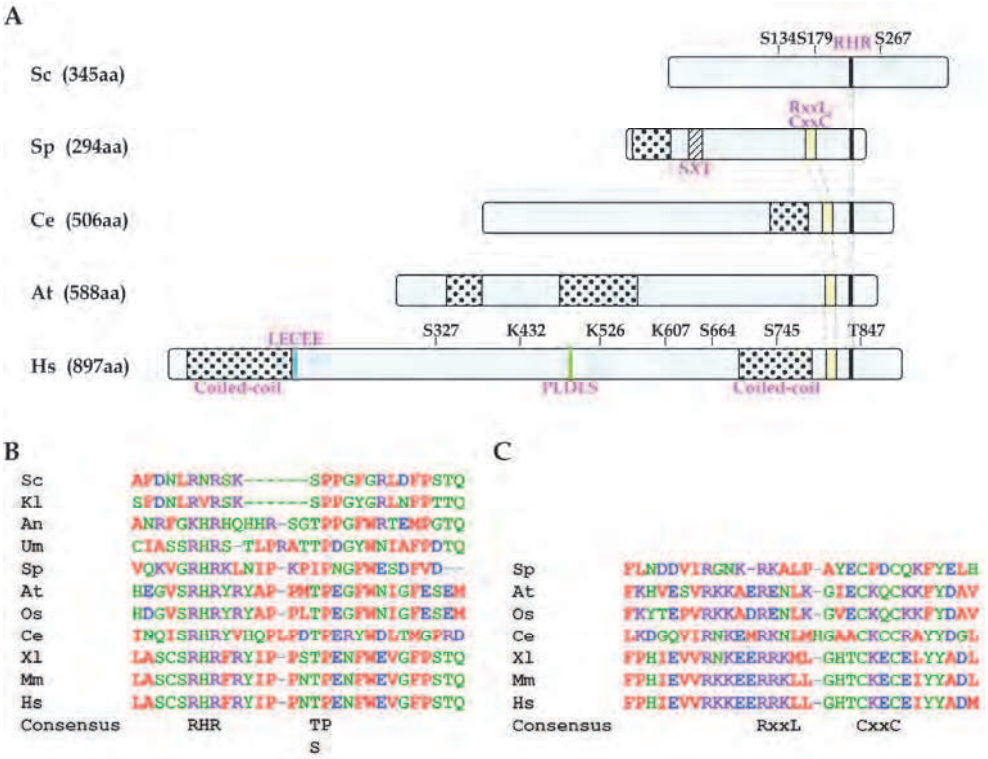


Fig. 1. (A) Schematic diagram of CtIP homologs. (B) Sequence alignment of the RHR motif and conserved CDK phosphorylation site. (C) Sequence alignment of the RxxL (D-box) and CxxC motifs. Kl, *Kluyveromyces lactis*; An, *Aspergillus nidulans*; Um, *Ustilago maydis*; Os, *Oryza sativa*; Xl, *Xenopus laevis*; Mm, *Mus musculus*; Hs, *Homo sapiens*.

not since been reported in any organism due to limited sequence similarity. The recent identification of SpCtp1 has led to the insight that it is homologous to proteins that have previously been characterized in several species such as ScSae2/Com1, CeCOM-1, AtGR1, and human CtIP (Limbo et al., 2007). In parallel, Jackson's group suggested that human CtIP shares some sequence homology with ScSae2 (Sartori et al., 2007). CtIP family proteins share several domains with highly conserved sequences but also demonstrate highly diverse sequences in other regions and show variety in protein length. These features might clarify why the orthologs were not recognized for a long time.

2.5 Domain structure of CtIP and its homologs

CtIP homologs retain C-terminal core domains, including RHR and CxxC motifs (Fig. 1A). The RHR motif is proposed to be the representative signature of Sae2/Com1 homologs (Limbo et al., 2007) and the limited 30 aa-region containing the RHR motif is well-conserved from ScSae2/Com1 to human CtIP (Fig. 1B). The CxxC motif is generally found in proteins with a D-box (RxxL) motif, which is representative among APC/C substrates, and the CxxC motif in some proteins is known to be involved in zinc chelation (Hopfner et al., 2002). The

CxxC and D-box motifs are conserved among CtIP homologs from fission yeast to humans with the exception of some other fungi, including *Saccharomyces* and *Aspergillus* (Fig. 1C). One or two coiled-coil motifs are also found in human CtIP and homologs from *S. pombe* and *A. thaliana*, but not in homologs from *C. elegans* or *S. cerevisiae* (Akamatsu et al., 2008; Limbo et al., 2007). The coiled-coil, LECEE and PLDLS motifs in human CtIP are required for dimerization (Dubin et al., 2004), Rb binding (Fusco et al., 1998) and CtBP binding (Schaeper et al., 1998), respectively. However, neither LECEE nor PLDLS motifs are found in the other homologs.

2.6 Posttranslational modifications of CtIP and its homologs

Several post-translational modification sites have been identified in CtIP homologs. Human CtIP has two CDK-dependent and two ATM-dependent phosphorylation sites. Phosphorylation at Ser-327 of CtIP by CDK increases around S/G_2 phases in unperturbed cells and might be responsible for CtIP-BRCA1 complex formation, which occurs in G_2 phase (Yu and Chen, 2004). Although this phosphorylation site does not seem to be conserved among species, another CDK-dependent site, Thr-847, which is likely to be conserved from yeast to humans, has been identified (Huertas and Jackson, 2009). Two ATM-target sites, Ser-664 and Ser-745, are phosphorylated in response to DNA damage, leading to Chk1 phosphorylation and the G_2/M transition checkpoint (Li et al., 2000). In addition to these phosphorylation events, CtIP is ubiquitinylated by the BRCA1-BARD1 heterodimer *in vivo* and *in vitro*. This ubiquitination is dependent on the RING domain of BRCA1 and phosphorylated Ser-327 of CtIP. Interestingly, the BRCA1-mediated ubiquitination does not target CtIP for degradation but for damage-induced foci formation (Yu et al., 2006). On the other hand, ubiquitin E3 ligase family protein, SIAH-1, is shown to interact with CtIP and promote its degradation (Germani et al., 2003). Therefore, ubiquitination of CtIP by SIAH-1 might be functionally different from that by BRCA1. Furthermore, it has been reported that CtIP is acetylated at Lys-432, Lys-526 and Lys-604 *in vivo*, and these acetylations are proposed to be important for the regulation of CtIP activity (Kaidi et al., 2010).

Similar to what has been observed in human CtIP, ScSae2 is phosphorylated periodically during the unperturbed cell cycle and in response to DNA damage (Baroni et al., 2004). Both cell cycle- and DNA damage-dependent Sae2 phosphorylation require the checkpoint kinase Mec1. Another pathway, involving Tel1 and MRX complex, is also required for full DNA damage-induced Sae2 phosphorylation (Baroni et al., 2004). Sae2 contains three potential CDK phosphorylation sites, Ser-134, Ser-179 and Ser-267, the last of which is a well-conserved residue that maps to the C-terminal region most highly conserved among organisms (Fig. 1C). Mutation of Ser-267 to an Ala residue causes phenotypes comparable to those observed in the *sae2*Δ null mutant (Huertas et al., 2008). Sae2 phosphorylation also occurs at the onset of premeiotic S phase, is maximal at the time of meiotic DSB generation and decreases when DSBs are repaired by homologous recombination, and is shown to be important to support the protein's meiotic recombination functions (Cartagena-Lirola et al., 2006). Recently, Sae2 was found to be acetylated and deacetylated, as seen in human CtIP (Robert et al., 2011).

In *S. pombe*, the CDK phosphorylation site corresponding to Ser-267 of ScSae2 has not been found, but Ctp1 contains two putative CDK-dependent phosphorylation sites and two putative Rad3/Tel1-dependent phosphorylation sites. Some of these sites have been suggested to be phosphorylated *in vivo*, whereas cells containing mutations in all of these sites show no obvious phenotype (Akamatsu et al., 2008). In addition, two putative Casein kinase 2 (CK2) phosphorylation sites (SXT motifs) are found in Ctp1 (Fig. 1C). It is still

unknown whether or not CK2 directly phosphorylates SXT motifs of Ctp1, though the phosphorylation of these motifs is essential for DNA damage repair *in vivo* and for binding with Nbs1 (Williams et al., 2009; Lloyd et al., 2009; Dodson et al., 2010) (See later). Phosphorylation by CK2 has not reported in other CtIP homologs to date.

3. CtIP and its homologs are involved in several biological processes

3.1 CtIP is involved in transcriptional regulation

As mentioned above, CtIP interacts with several proteins involved in transcriptional regulation, one of which is CtBP. CtBP acts as a transcriptional corepressor of several tumor suppressors such as E-cadherin, p16Ink4a, p15Ink4b, and PTEN, indicating a strong association with tumorigenesis and tumor progression (Chinnadurai, 2009). Complete transcriptional repression by CtIP requires binding to CtBP through its PLDLS domain (Meloni et al., 1999). The PLDLS motif of adenovirus E1A disrupts the CtBP-CtIP complex *in vitro*, which might potentiate the tumorigenesis-restraining activity of E1A exon 2 (Schaeper et al., 1998).

CtIP is also suggested to be a corepressor with Rb and p130 (Meloni et al., 1999). In contrast, CtIP has also been shown to bind Rb, allowing CtIP to bind its own promoter and an E2F target such as cyclin D1 during the G_1/S transition (Liu and Lee, 2006). This releases Rb-mediated transcriptional repression and increases the expression of genes required for S-phase entry. Furthermore, other groups have shown that CtIP can interact with the general transcription factors, TATA binding protein (TBP) and transcription factor IIB (Koipally and Georgopoulos, 2002). However, the functions of CtIP in transcriptional regulation might be limited to vertebrates and its orthologs might not play an important role in transcription.

3.2 Meiotic recombination and HR repair

In meiosis of *S. cerevisiae*, programmed DSBs are formed by a topoisomerase-like protein Spo11. Spo11 covalently attaches to the 5′ ends of the break, and a subsequent endonucleolytic step, dependent on the MRX complex, releases Spo11 bound to a short oligonucleotide (Neale et al., 2005). The MRX protein complex consists of Mre11, Rad50 and Xrs2 (Table 1) and is required for the formation of meiotic DSB and the processing of the DNA ends. Mre11 contains the phosphodiesterase motif responsible for nuclease activity. Rad50 contains Walker A and B motifs separated by a coiled-coil region and belongs to the SMC family proteins. The amino acid sequences of Mre11 and Rad50 are conserved among eukaryotes, while the amino acid sequence of Xrs2 is much less conserved. Its functional counterpart is called as Nbs1, exists among other eukaryotes, such as vertebrates, plants, nematodes and fission yeast (Rupnik et al., 2010). The degree of overall sequence similarity between Xrs2 and Nbs proteins is generally poor and homology is limited to an N-terminal forkhead-associated (FHA) domain and a small C-terminal region. Nbs1, but not Xrs2, contains a BRCT domain in the N-terminal region. It also forms a protein complex, MRN, similar to the MRX complex, which will henceforth be referred to as MRX(N).

S. cerevisiae rad50S mutations, separation-of-function mutations of *RAD50*, are defective in the processing of Spo11-induced DSBs and cause the accumulation of unprocessed DSBs with covalently attached Spo11 (Alani et al., 1990). The deletion mutants of the *sae2/com1* gene exhibit a meiotic-defective phenotype very similar to that of *rad50S* mutants, and Spo11-oligonucleotide complexes are not produced in either *rad50S* or *sae2*Δ/*com1*Δ mutants (Neale et al., 2002; Keeney and Kleckner, 1995). Similar observations were also made in *S.*

*pombe ctp1*Δ/*nip1*Δ cells (Hartsuiker et al., 2009a; Milman et al., 2009; Rothenberg et al., 2009; Akamatsu et al., 2008). Taken together with other results (Farah et al., 2009; Neale et al., 2002), yeast CtIP homologs are thought to be involved in DSB end resection in cooperation with the MRX(N) complex in meiosis.

During mitosis, *S. cerevisiae* mutants lacking either a component of the MRX complex or Sae2 exhibit sensitivity toward DNA-damaging agents and are defective in strand resection of DSB ends (McKee and Kleckner, 1997b; Clerici et al., 2005; Neale et al., 2005). In *S. pombe*, Ctp1 has been shown to function in an MRN-dependent HR repair pathway, but not in NHEJ (Akamatsu et al., 2008; Limbo et al., 2007). Chromatin immunoprecipitation (ChIP) assay of RPA at an HO-induced DSB site revealed that Ctp1, as well as Mre11, is required for DSB end resection (Limbo et al., 2007). These results are consistent with those from the Sae2 analysis. Additionally, ChIP assay showed that Ctp1 localizes to an HO-induced DSB site in a Mre11-dependent manner (Limbo et al., 2007). Thus, at least in fungi, the MRX(N) complex and CtIP homologs are implicated as cooperating in DSB end-processing during both mitotic and meiotic cell cycles. Furthermore, Ctp1 is required for the resection of the Top2-DNA complex, whereas Rad50 resects the Top1-DNA complex (Hartsuiker et al., 2009b). Recent analyses in *S. cerevisiae* revealed the requirement of Exo1, Sgs1, Top3, Rmi1 and Dna2 for processive DSB end resection (Mimitou and Symington, 2008; Zhu et al., 2008). The proteins involved in DSB end resection are listed in Table 1. One of these, Exo1, is a 5′-3′ exonuclease/flap endonuclease and another, Dna2, is an endonuclease with 5′-3′ helicase activity.

Sc	Sp	Hs	Note
Mre11	Rad32	MRE11	• single-strand endonuclease • 3′-5′ double-strand exonuclease • weak hairpin-opening activity
Rad50	Rad50	RAD50	• split ABC-type ATPase containing two heptad repeats • stimulates the 3′-5′ exonuclease and hairpin-opening activities of Mre11
Xrs2	Nbs1	NBS1	• contains an N-terminal FHA domain and a small C-terminal conserved domain • Nbs1, but not Xrs2, contains a BRCT domain in the N-terminal region • overall sequence similarity between Xrs2 and Nbs1 is weak and limited to an N-terminal FHA domain and a small C-terminal conserved domain
Sae2	Ctp1	CtIP	• endonuclease activity on single stranded DNA (Sae2) • stimulates nuclease activity of MR complex (Sae2 and CtIP)
Exo1	Exo1	EXO1	• 5′-3′ exonuclease, flap endonuclease
Sgs1	Rqh1	BLM	• RecQ family DNA helicase
Rmi1	Rmi1	RMI1 (BLAP75)	• RecQ-mediated genome instability protein • forms a complex with Sgs1 and Top3
Top3	Top3	TOPOIIIα	• type 1A topoisomerase
Dna2	Dna2	DNA2	• 5′-3′ helicase/endonuclease

Table 1. Proteins involved in DSB end resection.

Sgs1, a RecQ family helicase, forms a protein complex called RTR with Top3 and Rmi1. The RTR complex has multiple functions in DSB repair, including double Holliday junction dissolution (for review see (Ashton and Hickson, 2010)). The MRX complex and Sae2 in *S. cerevisiae* initiate 5′ degradation, leading to a subsequent step in which Exo1 and/or the RTR complex with Dna2 extensively degrade 5′ strands to generate long 3′ strands (Mimitou and Symington, 2008; Zhu et al., 2008). SpExo1 can substitute for Ctp1 on a *pku80*Δ background, suggesting that a similar mechanism may exist in *S. pombe* (Limbo et al., 2007).

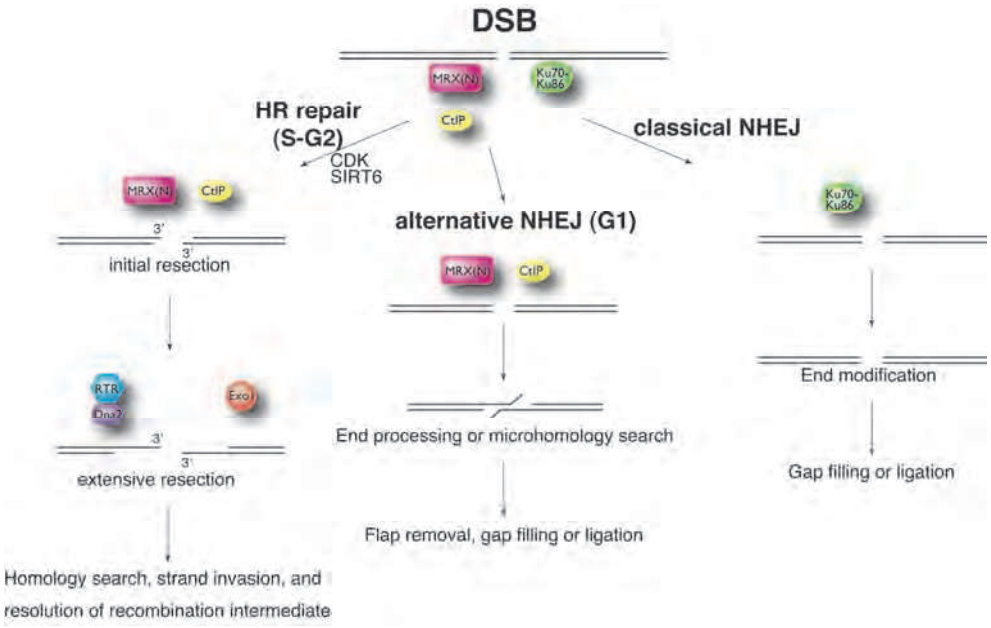


Fig. 2. Roles of CtIP/Sae2/Ctp1 in DSB repair.

Biochemically, Mre11 retains 3′->5′ exonuclease and ssDNA endonuclease and hairpin opening activities, all of which require Mn^{2+} as a metal cofactor (Trujillo and Sung, 2001; Sigurdsson et al., 2001). Both ATP and Rad50 stimulate the 3′->5′ exonuclease and hairpin opening activities of Mre11, where ATP is thought to regulate the DNA binding of the Mre11 complex via Rad50 (Trujillo and Sung, 2001). Remarkably, the ATP-dependent DNA end-resection reaction including the MRX complex, the RTR complex, Dna2 and the heterotrimeric ssDNA-binding protein RPA has been reconstituted (Cejka et al., 2010; Niu et al., 2010). Sae2 itself is shown to stimulate the nuclease activity of Mre11 and, interestingly, can cleave hairpin DNA, even in the absence of the MRX complex, at a cleavage site on the 3′ overhang adjacent to the hairpin (Lengsfeld et al., 2007). Recently, Paull and colleagues showed that MRX and Sae2 cooperatively promote Exo1-mediated 5′ strand degradation at DNA ends *in vitro*, but mutations in *RAD50*, *EXO1* or *MRE11* abrogate this end processing. Furthermore, *sae2* mutations reduce the efficiency of Exo1-mediated DSB resection both *in vitro* and *in vivo* (Nicolette et al., 2010). However, as neither the MRX complex or Sae2 have been shown to exhibit 5′->3′ exonuclease activity, it remains unclear how the generation of protruding 3′- ssDNA involves these proteins.

3.3 CtIP is involved in alternative NHEJ (A-NHEJ)

There are two varieties of NHEJ: classical-NHEJ (C-NHEJ) and alternative-NHEJ (A-NHEJ) (Zha et al., 2009). CtIP is required not only for HR repair in S/G_2 phase but also for A-NHEJ in G_1 upon generation of DSBs in human cells. The function of CtIP in A-NHEJ is independent of the phosphorylation of Ser-327 and recruitment of BRCA1. Cells expressing CtIP protein carrying mutations at Ser-327 are specifically defective in homologous recombination and show decreased levels of ssDNA after DNA damage, whereas A-NHEJ remains unaffected. Therefore, the phosphorylation of Ser-327 of CtIP is proposed to be a molecular switch to shift the balance of DSB repair from error-prone DNA end-joining to error-free homologous recombination in humans (Yun and Hiom, 2009).

3.4 Checkpoint control by CtIP-BRCA1 interaction

CtIP interacts with the BRCT motifs of BRCA1 in a manner dependent on the phosphorylation of Ser-327. The knockdown experiment shows that this interaction is required for DNA-damage-induced Chk1 phosphorylation and the G2/M transition checkpoint but not the damage-induced G2 accumulation checkpoint, for which BRCA1-BACH1 interaction is required. Therefore, the BRCA1 checkpoint pathway is divided into the BACH1-dependent pathway and the CtIP pathway (Yu and Chen, 2004). A crystal structure of the BRCT repeats in BRCA1 with a phosphopeptide corresponding to 322–333 residues of human CtIP has been solved (Varma et al., 2005). The BRCA1-CtIP interaction is ablated by several tumor-associated mutations affecting the BRCT motifs, suggesting that the interaction may be required for tumor suppression by BRCA1 (Liu et al., 1999; Wong et al., 1998; Yu et al., 1998). On the other hand, a sequence-based screen for mutations in the CtIP coding region in a panel of 89 tumor cell line cDNAs identified five missense variants (Wong et al., 1998). Therefore, CtIP itself may act as a tumor suppressor in human cells.

The MRN complex senses DSBs and activates the ataxia-telangiectasia mutated (ATM) kinase, resulting in a DNA damage response in human cells (Lee and Paull, 2004; Uziel et al., 2003). Similarly, the MRN(X) complex is required for the activation of the ATM ortholog, Tel1, in both *S. cerevisiae* and *S. pombe* (You et al., 2005; D'Amours and Jackson, 2001). Upon activation, ATM and its orthologs phosphorylate downstream substrates such as Mre11, Nbs1/Xrs2 and CtIP/Sae2 (Rupnik et al., 2010) (and see above). In contrast to the MRN(X) complex, CtIP and its homologs seem not to be involved in checkpoint activation (Limbo et al., 2007).

Interestingly, Sae2 has been shown to be required for proper recovery from checkpoint-mediated cell cycle arrest after DNA damage in *S. cerevisiae* (Clerici et al., 2006). However, the phenomenon of recovery from cell cycle arrest or the involvement of Sae2 homologs in this phenomenon has not been reported in organisms other than *S. cerevisiae*.

4. Functional regulation of CtIP and its homologs

4.1 Interaction with Nbs1 regulates CtIP

The N-terminal region of Nbs1 contains FHA and BRCT motifs, both of which are known to be phosphopeptide-binding protein modules. Recently, the crystal structure of SpNbs1 has revealed that the FHA domain of Nbs1 is fused directly to the tandem BRCT domain, leading to consideration of the functional interactions of CtIP with Mre11-Rad50 through Nbs1 (Lloyd et al., 2009; Williams et al., 2008).

SpCtp1 was shown to genetically interact with SpNbs1 in *S. pombe* and the FHA domain of SpNbs1 was implicated to play an important role in this interaction (Akamatsu et al., 2008). CtIP was also reported to interact with the MRN complex (Sartori et al., 2007) and, subsequently, it was demonstrated that recombinant CtIP prepared from insect cells binds directly to hNBS1 (Chen et al., 2008).

The FHA domain of hNBS1 interacts with phosphorylated SDT sites on hMDC1, whose sequence is a recognition motif for CK2 (Chapman and Jackson, 2008; Melander et al., 2008; Spycher et al., 2008). The FHA domain of SpNbs1, which is also important for cellular survival upon treatment with DNA damaging agents, is essential for Ctp1-binding *in vivo* (Lloyd et al., 2009; Williams et al., 2008). Interestingly, mutations in the SXT sites in Ctp1 sensitize cells to DNA damage and disrupt interactions with Nbs1, indicating that the interaction of Nbs1 and the phosphorylated SDT sites of Ctp1 through FHA is essential for DNA damage repair (Dodson et al., 2010). Although it has yet to be addressed whether or not CK2 directly phosphorylates the SXT sites of Ctp1, the crystal structure of the SpNbs1 bound to the phosphopeptide at a SXT site on Ctp1 has shown that the phosphorylation of the SXT sites is a prerequisite for the complex formation (Lloyd et al., 2009; Williams et al., 2008).

The interface of the association of Nbs1 with Mre11 maps to the C-terminal region in Nbs1 (You et al., 2005; Falck et al., 2005) and the interface of Mre11 dimerization is located away from the DNA-binding cleft (Williams et al., 2008).

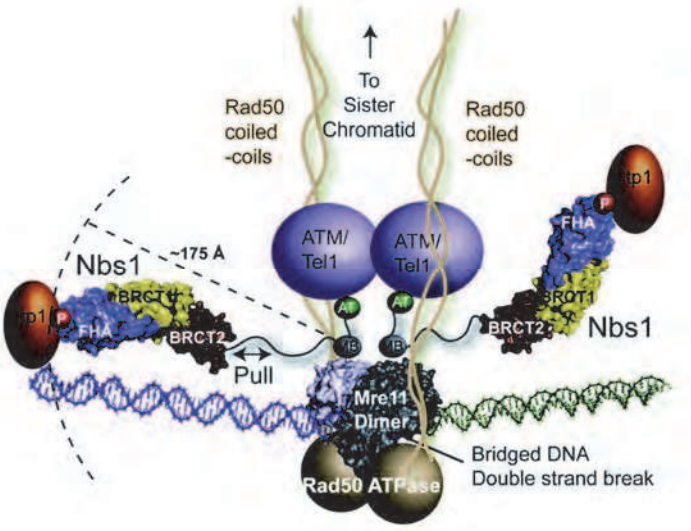


Fig. 3. Model of the MRN-Ctp1 complex bound at a bridging DNA DSB as proposed by (Williams et al., 2008). The flexible Nbs1 C-terminus links FHA-bound Ctp1 to an Mre11-Rad50 heterotetrameric core complex bridging a DSB.

The distance from the Mre11 binding domain to the N-terminal FHA domain was determined to be ~175 Å, as assessed by SAXS and X-ray crystallography (Lloyd et al., 2009; Williams et al., 2008). The MRN complex and Ctp1 colocalize to within ~200 bp (<700 Å) of a

single DSB site cleaved by a defined endonuclease *in vivo*. Based on this geometry and other evidence, a model has been proposed in which the flexible Nbs1 C-terminus links the FHA-bound Ctp1 to an Mre11-Rad50 heterotetrameric core complex, bridging two ends of a DSB (Williams et al., 2008) (Fig. 3). The model effectively accounts for recent insights into the roles of the Mre11-Rad50 heterotetrameric core at a DSB end (Williams et al., 2008; Chen et al., 2001; Hopfner et al., 2002; 2001; Moreno-Herrero et al., 2005).

4.2 CtIP homologs are highly regulated in the cell cycle

Gene expression of human and mouse CtIP proteins increases during G_1 to S phase (Liu and Lee, 2006). SpCtp1 is periodically transcribed in S phase and is regarded as one of the putative MBF-regulated genes (Limbo et al., 2007). This role in transcriptional regulation and the other functions of CtIP and its homologs seem to be regulated posttranslationally. As previously mentioned, the mechanism regulating homologous recombination by CDK is conserved between human and budding yeast cells; however, the corresponding CDK phosphorylation site has not been found in SpCtp1. The regulation of Ctp1 by CDK might not be absolutely necessary as G_1 phase is relatively short in *S. pombe*.

Recently, it has been found that CtIP and Sae2 are also modified by acetylation. Jackson's group found that CtIP is constitutively acetylated but is deacetylated by SIRT6 upon treatment with a DNA damaging agent (Kaidi et al., 2010). SIRT6 is an NAD^+ (nicotinamide adenine dinucleotide)-dependent sirtuin (class III), a member of the family of protein lysin deacetylases (KDACs). CtIP was identified as a target protein of SIRT6 and it was shown that deacetylation of CtIP by SIRT6 is an important regulatory event in DSB end processing.

On the other hand, Foiani's group revealed that treatment with the HDAC inhibitor, valproic acid (VPA), causes DSB processing defects in *S. cerevisiae* (Robert et al., 2011). Upon VPA treatment, acetylation levels of Sae2 increased and Sae2 was degraded. Rapamycin treatment induced Sae2 degradation through autophagy, and mutations in the genes involved in autophagy rescued Sae2 levels. Furthermore, two HDACs (Rpd3 and Hda1) and one HAT (Gcn5) influenced Sae2 turnover. It is not known whether Sae2 is directly acetylated/deacetylated by these HAT and HDACs. However, it is indisputable that the acetylation of CtIP homologs plays an important role in the regulation of DSB end resection in both human and yeast cells.

5. Conclusion

As DSBs can ultimately have toxic effects on cells, such as chromosome translocation, deletion, or duplication, they must be repaired appropriately. Cells utilize several damage responses depending on the cell-cycle phase. CtIP (and its orthologs) is one of the most important key players in the initial steps of DSB repair, in which cells determine the appropriate repair pathway and process the DSB ends. In addition, the importance of posttranslational modifications of CtIP is now being elucidated. However, the precise molecular mechanism of the generation of the recombinogenic 3′ ssDNA overhang by the combined actions of CtIP/Ctp1/Sae2 and the MRN(X) complex still remains unclear.

CtIP and many of its binding partners, such as BRCA1, CtBP and Rb, are classified as tumor suppressors. Furthermore, NBS1 and MRE11 are associated with Nijmegen breakage syndrome (NBS) and ataxia-telangiectasia-like disorder (ATLD), respectively, both of which

are chromosome instability syndromes. Cells carrying mutations in either of these genes show DNA damage hyper-sensitivity (Carney et al., 1998; Stewart et al., 1999). Taken together, these facts illustrate not only the scientific interest but also the clinical importance of understanding the molecular mechanism of DSB end resection mediated by MRN(X) and CtIP (or its orthologs).

6. Acknowledgments

Our study was supported by Grants-in-Aid for Scientific Research on Priority Innovative Areas from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and for Scientific Research (A).

7. References

Akamatsu, Y., Murayama, Y., Yamada, T., Nakazaki, T., Tsutsui, Y., Ohta, K., and Iwasaki, H. (2008). Molecular characterization of the role of the *Schizosaccharomyces pombe nip1+/ctp1+* gene in DNA double-strand break repair in association with the Mre11-Rad50-Nbs1 complex. Mol Cell Biol *28*, 3639-3651.

Alani, E., Padmore, R., and Kleckner, N. (1990). Analysis of wild-type and *rad50* mutants of yeast suggests an intimate relationship between meiotic chromosome synapsis and recombination. Cell *61*, 419-436.

Ashton, T. M., and Hickson, I. D. (2010). Yeast as a model system to study RecQ helicase function. DNA Repair *9*, 303-314.

Baroni, E., Viscardi, V., Cartagena-Lirola, H., Lucchini, G., and Longhese, M. P. (2004). The functions of budding yeast Sae2 in the DNA damage response require Mec1- and Tel1-dependent phosphorylation. Mol Cell Biol *24*, 4151-4165.

Boyd, J. M., Subramanian, T., Schaeper, U., La Regina, M., Bayley, S., and Chinnadurai, G. (1993). A region in the C-terminus of adenovirus 2/5 E1a protein is required for association with a cellular phosphoprotein and important for the negative modulation of T24-ras mediated transformation, tumorigenesis and metastasis. EMBO J *12*, 469-478.

Carney, J. P., Maser, R. S., Olivares, H., Davis, E. M., Le Beau, M., Yates, J. R., Hays, L., Morgan, W. F., and Petrini, J. H. (1998). The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. Cell *93*, 477-486.

Cartagena-Lirola, H., Guerini, I., Viscardi, V., Lucchini, G., and Longhese, M. P. (2006). Budding Yeast Sae2 is an In Vivo Target of the Mec1 and Tel1 Checkpoint Kinases During Meiosis. Cell Cycle *5*, 1549-1559.

Cejka, P., Cannavo, E., Polaczek, P., Masuda-Sasa, T., Pokharel, S., Campbell, J. L., and Kowalczykowski, S. C. (2010). DNA end resection by Dna2-Sgs1-RPA and its stimulation by Top3-Rmi1 and Mre11-Rad50-Xrs2. Nature *467*, 112-116.

Chapman, J. R., and Jackson, S. P. (2008). Phospho-dependent interactions between NBS1 and MDC1 mediate chromatin retention of the MRN complex at sites of DNA damage. EMBO Rep *9*, 795-801.

Chen, L., Nievera, C. J., Lee, A. Y., and Wu, X. (2008). Cell cycle-dependent complex formation of BRCA1.CtIP.MRN is important for DNA double-strand break repair. J Biol Chem *283*, 7713-7720.

Chen, L., Trujillo, K., Ramos, W., Sung, P., and Tomkinson, A. E. (2001). Promotion of Dnl4-catalyzed DNA end-joining by the Rad50/Mre11/Xrs2 and Hdf1/Hdf2 complexes. Mol Cell *8*, 1105-1115.

Chinnadurai, G. (2009). The transcriptional corepressor CtBP: a foe of multiple tumor suppressors. Cancer Res *69*, 731-734.

Clerici, M., Mantiero, D., Lucchini, G., and Longhese, M. P. (2006). The *Saccharomyces cerevisiae* Sae2 protein negatively regulates DNA damage checkpoint signalling. EMBO Rep *7*, 212-218.

Clerici, M., Mantiero, D., Lucchini, G., and Longhese, M. P. (2005). The *Saccharomyces cerevisiae* Sae2 protein promotes resection and bridging of double strand break ends. J Biol Chem *280*, 38631-38638.

D'Amours, D., and Jackson, S. P. (2001). The yeast Xrs2 complex functions in S phase checkpoint regulation. Genes Dev *15*, 2238-2249.

Deveaux, Y., Alonso, B., Pierrugues, O., Godon, C., and Kazmaier, M. (2000). Molecular cloning and developmental expression of AtGR1, a new growth-related Arabidopsis gene strongly induced by ionizing radiation. Radiat Res *154*, 355-364.

Dodson, G. E., Limbo, O., Nieto, D., and Russell, P. (2010). Phosphorylation-regulated binding of Ctp1 to Nbs1 is critical for repair of DNA double-strand breaks. Cell Cycle *9*.

Dubin, M. J., Stokes, P. H., Sum, E. Y. M., Williams, R. S., Valova, V. A., Robinson, P. J., Lindeman, G. J., Glover, J. N. M., Visvader, J. E., and Matthews, J. M. (2004). Dimerization of CtIP, a BRCA1- and CtBP-interacting protein, is mediated by an N-terminal coiled-coil motif. J Biol Chem *279*, 26932-26938.

Falck, J., Coates, J., and Jackson, S. P. (2005). Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. Nature *434*, 605-611.

Farah, J. A., Cromie, G. A., and Smith, G. R. (2009). Ctp1 and Exonuclease 1, alternative nucleases regulated by the MRN complex, are required for efficient meiotic recombination. Proceedings of the National Academy of Sciences *106*, 9356-9361.

Fusco, C., Reymond, A., and Zervos, A. S. (1998). Molecular cloning and characterization of a novel retinoblastoma-binding protein. Genomics *51*, 351-358.

Germani, A., Prabel, A., Mourah, S., Podgorniak, M., Di Carlo, A., Ehrlich, R., Gisselbrecht, S., Varin-Blank, N., Calvo, F., and Bruzzoni-Giovanelli, H. (2003). SIAH-1 interacts with CtIP and promotes its degradation by the proteasome pathway. Oncogene *22*, 8845-8851.

Gönczy, P., Schnabel, H., Kaletta, T., Amores, A. D., Hyman, T., and Schnabel, R. (1999). Dissection of cell division processes in the one cell stage *Caenorhabditis elegans* embryo by mutational analysis. J Cell Biol *144*, 927-946.

Hartsuiker, E., Mizuno, K., Molnar, M., Kohli, J., Ohta, K., and Carr, A. M. (2009a). Ctp1^{CtIP} and Rad32^{Mre11} nuclease activity are required for Rec12^{Spo11} removal, but Rec12^{Spo11} removal is dispensable for other MRN-dependent meiotic functions. Mol Cell Biol *29*, 1671-1681.

Hartsuiker, E., Neale, M. J., and Carr, A. M. (2009b). Distinct requirements for the Rad32^{Mre11} nuclease and Ctp1^{CtIP} in the removal of covalently bound topoisomerase I and II from DNA. Mol Cell *33*, 117-123.

Hopfner, K., Craig, L., Moncalian, G., Zinkel, R. A., Usui, T., Owen, B. A. L., Karcher, A., Henderson, B., Bodmer, J., McMurray, C. T., et al. (2002). The Rad50 zinc-hook is a

structure joining Mre11 complexes in DNA recombination and repair. Nature *418*, 562-566.

Hopfner, K. P., Karcher, A., Craig, L., Woo, T. T., Carney, J. P., and Tainer, J. A. (2001). Structural biochemistry and interaction architecture of the DNA double-strand break repair Mre11 nuclease and Rad50-ATPase. Cell *105*, 473-485.

Huertas, P., Cortés-Ledesma, F., Sartori, A. A., Aguilera, A., and Jackson, S. P. (2008). CDK targets Sae2 to control DNA-end resection and homologous recombination. Nature *455*, 689-692.

Huertas, P., and Jackson, S. P. (2009). Human CtIP mediates cell cycle control of DNA end resection and double strand break repair. J Biol Chem *284*, 9558-9565.

Kaidi, A., Weinert, B. T., Choudhary, C., and Jackson, S. P. (2010). Human SIRT6 promotes DNA end resection through CtIP deacetylation. Science *329*, 1348-1353.

Keeney, S., and Kleckner, N. (1995). Covalent protein-DNA complexes at the 5' strand termini of meiosis-specific double-strand breaks in yeast. Proc Natl Acad Sci USA *92*, 11274-11278.

Koipally, J., and Georgopoulos, K. (2002). Ikaros-CtIP interactions do not require C-terminal binding protein and participate in a deacetylase-independent mode of repression. J Biol Chem *277*, 23143-23149.

Lee, J., and Paull, T. T. (2004). Direct activation of the ATM protein kinase by the Mre11/Rad50/Nbs1 complex. Science *304*, 93-96.

Lengsfeld, B. M., Rattray, A. J., Bhaskara, V., Ghirlando, R., and Paull, T. T. (2007). Sae2 is an endonuclease that processes hairpin DNA cooperatively with the Mre11/Rad50/Xrs2 complex. Mol Cell *28*, 638-651.

Li, S., Chen, P. L., Subramanian, T., Chinnadurai, G., Tomlinson, G., Osborne, C. K., Sharp, Z. D., and Lee, W. H. (1999). Binding of CtIP to the BRCT repeats of BRCA1 involved in the transcription regulation of p21 is disrupted upon DNA damage. J Biol Chem *274*, 11334-11338.

Li, S., Ting, N. S., Zheng, L., Chen, P. L., Ziv, Y., Shiloh, Y., Lee, E. Y., and Lee, W. H. (2000). Functional link of BRCA1 and ataxia telangiectasia gene product in DNA damage response. Nature *406*, 210-215.

Limbo, O., Chahwan, C., Yamada, Y., de Bruin, R. A. M., Wittenberg, C., and Russell, P. (2007). Ctp1 is a cell-cycle-regulated protein that functions with Mre11 complex to control double-strand break repair by homologous recombination. Mol Cell *28*, 134-146.

Liu, F., and Lee, W. (2006). CtIP activates its own and cyclin D1 promoters via the E2F/RB pathway during G1/S progression. Mol Cell Biol *26*, 3124-3134.

Liu, Z., Macias, M., Bottomley, M., Stier, G., Linge, J., Nilges, M., Bork, P., and Sattler, M. (1999). The three-dimensional structure of the HRDC domain and implications for the Werner and Bloom syndrome proteins. Structure *7*, 1557-1566.

Lloyd, J., Chapman, J. R., Clapperton, J. A., Haire, L. F., Hartsuiker, E., Li, J., Carr, A. M., Jackson, S. P., and Smerdon, S. J. (2009). A supramodular FHA/BRCT-repeat architecture mediates Nbs1 adaptor function in response to DNA damage. Cell *139*, 100-111.

McKee, A. H., and Kleckner, N. (1997a). A general method for identifying recessive diploid-specific mutations in *Saccharomyces cerevisiae*, its application to the isolation of

mutants blocked at intermediate stages of meiotic prophase and characterization of a new gene *SAE2*. Genetics *146*, 797-816.

McKee, A. H., and Kleckner, N. (1997b). Mutations in *Saccharomyces cerevisiae* that block meiotic prophase chromosome metabolism and confer cell cycle arrest at pachytene identify two new meiosis-specific genes *SAE1* and *SAE3*. Genetics *146*, 817-834.

Melander, F., Bekker-Jensen, S., Falck, J., Bartek, J., Mailand, N., and Lukas, J. (2008). Phosphorylation of SDT repeats in the MDC1 N terminus triggers retention of NBS1 at the DNA damage-modified chromatin. J Cell Biol *181*, 213-226.

Meloni, A. R., Smith, E. J., and Nevins, J. R. (1999). A mechanism for Rb/p130-mediated transcription repression involving recruitment of the CtBP corepressor. Proc Natl Acad Sci USA *96*, 9574-9579.

Milman, N., Higuchi, E., and Smith, G. R. (2009). Meiotic DNA double-strand break repair requires two nucleases, MRN and Ctp1, to produce a single size class of Rec12 (Spo11)-oligonucleotide complexes. Mol Cell Biol *29*, 5998-6005.

Mimitou, E. P., and Symington, L. S. (2008). Sae2, Exo1 and Sgs1 collaborate in DNA double-strand break processing. Nature *455*, 770-774.

Moreno-Herrero, F., de Jager, M., Dekker, N. H., Kanaar, R., Wyman, C., and Dekker, C. (2005). Mesoscale conformational changes in the DNA-repair complex Rad50/Mre11/Nbs1 upon binding DNA. Nature *437*, 440-443.

Neale, M. J., Pan, J., and Keeney, S. (2005). Endonucleolytic processing of covalent protein-linked DNA double-strand breaks. Nature *436*, 1053-1057.

Neale, M. J., Ramachandran, M., Trelles-Sticken, E., Scherthan, H., and Goldman, A. S. H. (2002). Wild-type levels of Spo11-induced DSBs are required for normal single-strand resection during meiosis. Mol Cell *9*, 835-846.

Nicolette, M. L., Lee, K., Guo, Z., Rani, M., Chow, J. M., Lee, S. E., and Paull, T. T. (2010). Mre11-Rad50-Xrs2 and Sae2 promote 5' strand resection of DNA double-strand breaks. Nat Struct Mol Biol *17*, 1478-1485.

Niu, H., Chung, W., Zhu, Z., Kwon, Y., Zhao, W., Chi, P., Prakash, R., Seong, C., Liu, D., Lu, L., et al. (2010). Mechanism of the ATP-dependent DNA end-resection machinery from Saccharomyces cerevisiae. Nature *467*, 108-111.

Penkner, A., Portik-Dobos, Z., Tang, L., Schnabel, R., Novatchkova, M., Jantsch, V., and Loidl, J. (2007). A conserved function for a *Caenorhabditis elegans* Com1/Sae2/CtIP protein homolog in meiotic recombination. EMBO J *26*, 5071-5082.

Prinz, S., Amon, A., and Klein, F. (1997). Isolation of *COM1*, a new gene required to complete meiotic double-strand break-induced recombination in *Saccharomyces cerevisiae*. Genetics *146*, 781-795.

Robert, T., Vanoli, F., Chiolo, I., Shubassi, G., Bernstein, K. A., Rothstein, R., Botrugno, O. A., Parazzoli, D., Oldani, A., Minucci, S., et al. (2011). HDACs link the DNA damage response, processing of double-strand breaks and autophagy. Nature *471*, 74-79.

Rothenberg, M., Kohli, J., and Ludin, K. (2009). Ctp1 and the MRN-complex are required for endonucleolytic Rec12 removal with release of a single class of oligonucleotides in fission yeast. PLoS Genet *5*, e1000722.

Rupnik, A., Lowndes, N. F., and Grenon, M. (2010). MRN and the race to the break. Chromosoma *119*, 115-135.

Sartori, A. A., Lukas, C., Coates, J., Mistrik, M., Fu, S., Bartek, J., Baer, R., Lukas, J., and Jackson, S. P. (2007). Human CtIP promotes DNA end resection. Nature *450*, 509-514.

Schaeper, U., Subramanian, T., Lim, L., Boyd, J. M., and Chinnadurai, G. (1998). Interaction between a cellular protein that binds to the C-terminal region of adenovirus E1A (CtBP) and a novel cellular protein is disrupted by E1A through a conserved PLDLS motif. J Biol Chem *273*, 8549-8552.

Schaeper, U., Boyd, J. M., Verma, S., Uhlmann, E., Subramanian, T., and Chinnadurai, G. (1995). Molecular cloning and characterization of a cellular phosphoprotein that interacts with a conserved C-terminal domain of adenovirus E1A involved in negative modulation of oncogenic transformation. Proc Natl Acad Sci USA *92*, 10467-10471.

Sigurdsson, S., Trujillo, K., Song, B., Stratton, S., and Sung, P. (2001). Basis for avid homologous DNA strand exchange by human Rad51 and RPA. J Biol Chem *276*, 8798-8806.

Spycher, C., Miller, E. S., Townsend, K., Pavic, L., Morrice, N. A., Janscak, P., Stewart, G. S., and Stucki, M. (2008). Constitutive phosphorylation of MDC1 physically links the MRE11-RAD50-NBS1 complex to damaged chromatin. J Cell Biol *181*, 227-240.

Stewart, G. S., Maser, R. S., Stankovic, T., Bressan, D. A., Kaplan, M. I., Jaspers, N. G., Raams, A., Byrd, P. J., Petrini, J. H., and Taylor, A. M. (1999). The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. Cell *99*, 577-587.

Sum, E. Y. M., Peng, B., Yu, X., Chen, J., Byrne, J., Lindeman, G. J., and Visvader, J. E. (2002). The LIM domain protein LMO4 interacts with the cofactor CtIP and the tumor suppressor BRCA1 and inhibits BRCA1 activity. J Biol Chem *277*, 7849-7856.

Trujillo, K. M., and Sung, P. (2001). DNA structure-specific nuclease activities in the *Saccharomyces cerevisiae* Rad50*Mre11 complex. J Biol Chem *276*, 35458-35464.

Uziel, T., Lerenthal, Y., Moyal, L., Andegeko, Y., Mittelman, L., and Shiloh, Y. (2003). Requirement of the MRN complex for ATM activation by DNA damage. EMBO J *22*, 5612-5621.

Varma, A. K., Brown, R. S., Birrane, G., and Ladias, J. A. A. (2005). Structural basis for cell cycle checkpoint control by the BRCA1-CtIP complex. Biochemistry *44*, 10941-10946.

Williams, R. S., Moncalian, G., Williams, J. S., Yamada, Y., Limbo, O., Shin, D. S., Groocock, L. M., Cahill, D., Hitomi, C., Guenther, G., et al. (2008). Mre11 dimers coordinate DNA end bridging and nuclease processing in double-strand-break repair. Cell *135*, 97-109.

Williams, R. S., Dodson, G. E., Limbo, O., Yamada, Y., Williams, J. S., Guenther, G., Classen, S., Glover, J. N. M., Iwasaki, H., Russell, P., et al. (2009). Nbs1 flexibly tethers Ctp1 and Mre11-Rad50 to coordinate DNA double-strand break processing and repair. Cell *139*, 87-99.

Wong, A. K., Ormonde, P. A., Pero, R., Chen, Y., Lian, L., Salada, G., Berry, S., Lawrence, Q., Dayananth, P., Ha, P., et al. (1998). Characterization of a carboxy-terminal BRCA1 interacting protein. Oncogene *17*, 2279-2285.

You, Z., Chahwan, C., Bailis, J., Hunter, T., and Russell, P. (2005). ATM activation and its recruitment to damaged DNA require binding to the C terminus of Nbs1. Mol Cell Biol *25*, 5363-5379.

Yu, X., Fu, S., Lai, M., Baer, R., and Chen, J. (2006). BRCA1 ubiquitinates its phosphorylation-dependent binding partner CtIP. Genes Dev *20*, 1721-1726.

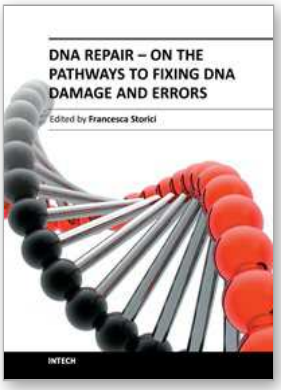
Yu, X., Wu, L. C., Bowcock, A. M., Aronheim, A., and Baer, R. (1998). The C-terminal (BRCT) domains of BRCA1 interact in vivo with CtIP, a protein implicated in the CtBP pathway of transcriptional repression. J Biol Chem *273*, 25388-25392.

Yu, X., and Chen, J. (2004). DNA damage-induced cell cycle checkpoint control requires CtIP, a phosphorylation-dependent binding partner of BRCA1 C-terminal domains. Mol Cell Biol *24*, 9478-9486.

Yun, M. H., and Hiom, K. (2009). CtIP-BRCA1 modulates the choice of DNA double-strand-break repair pathway throughout the cell cycle. Nature *459*, 460-463.

Zha, S., Boboila, C., and Alt, F. W. (2009). Mre11: roles in DNA repair beyond homologous recombination. Nat Struct Mol Biol *16*, 798-800.

Zhu, Z., Chung, W., Shim, E. Y., Lee, S. E., and Ira, G. (2008). Sgs1 helicase and two nucleases Dna2 and Exo1 resect DNA double-strand break ends. Cell *134*, 981-994.



DNA Repair - On the Pathways to Fixing DNA Damage and Errors

Edited by Dr. Francesca Storici

ISBN 978-953-307-649-2
Hard cover, 380 pages
Publisher InTech
Published online 09, September, 2011
Published in print edition September, 2011

DNA repair is fundamental to all cell types to maintain genomic stability. A collection of cutting-edge reviews, DNA Repair - On the pathways to fixing DNA damage and errors covers major aspects of the DNA repair processes in a large variety of organisms, emphasizing foremost developments, questions to be solved and new directions in this rapidly evolving area of modern biology. Written by researchers at the vanguard of the DNA repair field, the chapters highlight the importance of the DNA repair mechanisms and their linkage to DNA replication, cell-cycle progression and DNA recombination. Major topics include: base excision repair, nucleotide excision repair, mismatch repair, double-strand break repair, with focus on specific inhibitors and key players of DNA repair such as nucleases, ubiquitin-proteasome enzymes, poly ADP-ribose polymerase and factors relevant for DNA repair in mitochondria and embryonic stem cells. This book is a journey into the cosmos of DNA repair and its frontiers.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yasuhiro Tsutsui, Akihito Kawasaki and Hiroshi Iwasaki (2011). Human CtIP and Its Homologs: Team Players in DSB Resection Games, DNA Repair - On the Pathways to Fixing DNA Damage and Errors, Dr. Francesca Storici (Ed.), ISBN: 978-953-307-649-2, InTech, Available from: http://www.intechopen.com/books/dna-repair-on-the-pathways-to-fixing-dna-damage-and-errors/human-ctip-and-its-homologs-team-players-in-dsb-resection-games

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821