Effect of Amino Acid Substitutions in the Rad50 ATP Binding Domain on DNA Double Strand Break Repair in Yeast*

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The Saccharomyces cerevisiae Rad50-Mre11-Xrs2 complex plays a central role in the cellular response to DNA double strand breaks. Rad50 has a globular ATPase head domain with a long coiled-coil tail. DNA binding by Rad50 is ATP-dependent and the Rad50-Mre11-Xrs2 complex possesses DNA unwinding and endonuclease activities that are regulated by ATP. Here we have examined the role of the Rad50 Walker type A ATP binding motif in DNA double strand break repair by a combination of genetic and biochemical approaches. Replacement of the conserved lysine residue within the Walker A motif with alanine, glutamate, or arginine results in the same DNA damage sensitivity and homologous recombination defect as the rad50 deletion mutation. The Walker A mutations also cause a deficiency in non-homologous end-joining. As expected, complexes containing the rad50 Walker A mutant proteins are defective in ATPase, ATP-dependent DNA unwinding, and ATP-stimulated endonuclease activities. Although the DNA end-bridging activity of the Rad50-Mre11-Xrs2 complex is ATP-independent, the end-bridging activity of complexes containing the rad50 Walker A mutant proteins is salt-sensitive. These results provide a molecular explanation for the observed in vivo defects of the rad50 Walker mutant strains and reveal a novel ATP-independent function for Rad50 in DNA end-bridging.

DNA double strand breaks (DSBs) arise from a variety of sources including normal physiological programs, such as DNA damage. These lesions are highly cytotoxic and mutagenic, and their removal is mediated by homologous recombination (HR) and non-homologous end-joining (NHEJ). Genetic and biochemical studies have led to the identification of many components of these two DNA repair pathways. Although HR and NHEJ mostly involve unique sets of protein factors, the yeast Rad50-Mre11-Xrs2 (RMX) complex has been implicated in both pathways. In addition, this evolutionarily conserved protein complex participates in telomere maintenance, DNA damage-activated cell cycle checkpoints, the release of Spo11 protein from meiotic DSBs, and possibly sister chromatid cohesion.

The Rad50cd protein may be important for the RMX complex to bridge DSBs in mitotic cells to yield single-stranded DNA tails to be used by the HR machinery to initiate recombinational repair. Accordingly, the DNA damage sensitivity of strains lacking a functional RMX complex is suppressed by overexpressing ExoI, a 5'→3' exonuclease.

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molecules via zinc chelation (6). ATP binding stimulates DNA binding by Rad50 (15, 18). Notably, analyses of complexes containing Rad50 have revealed ATP-dependent modulation of the Mre11 nuclease activity and an ATP-dependent DNA unwinding activity (9, 10, 19).

The third subunit of the Mre11-associated protein complex, Xrs2 in yeast and NBS1 in humans, is less well characterized. Phosphorylation of Xrs2 and NBS1 by the DNA damage checkpoint kinases is consistent with this subunit being required for DNA damage-activated signal transduction pathways (10, 20–24). Furthermore, the presence of protein-protein interaction modules in Xrs2/Nbs1 implicates it in the recruitment of other protein factors (25–27). In support of this notion, a physical interaction between Xrs2 and the Lif1 subunit of Dnl4/Lif1 has been demonstrated (13). Recent studies have revealed that Xrs2 is a DNA structure-specific-binding protein and that it is indispensable for DNA end engagement and ATP-dependent DNA unwinding by the RMX complex (10).

We have employed a combination of genetic and biochemical approaches to determine how ATP influences the biological functions of Rad50 and the RMX complex. Importantly, mutations that alter the conserved lysine residue in the Walker type A motif of yeast Rad50 impair both HR and NHEJ. Biochemically, the rad50 Walker mutations inactivate the ATPase activity of the RMX complex and lead to the loss of the ATP-dependent DNA structure-specific endonuclease and DNA unwinding activities of this complex as well. Even though the DNA end binding and end-bridging activities of the RMX complex are not influenced by ATP, we demonstrate that the Walker A motif itself is important for DNA end-bridging and DNA end-joining when a physiological level of salt is present. Our results provide molecular information concerning the role of ATP in RMX functions and also implicate the region in Rad50 protein that encompasses the Walker A motif in DNA end-bridging and DNA end-joining independent of ATP.

EXPERIMENTAL PROCEDURES

Construction of Yeast Strains—The strain W1588-4C (MATa ade2-1 can1-100 leu2-3,112 his3-11,15 ura3-1 trp1-1 RAD50) was used for the integration of mutant alleles at the RAD50 locus. The integrating plasmids with mutations in the codon for lysine 40 were site-directed mutagenesis of YIp5::RAD50 containing the RAD50 open reading frame inserted in the BamHI site and carrying the URA3 marker. The rad50 mutant alleles were sequenced to ensure that no untemplated bases had been introduced. To maintain the rad50 mutations, wild-type and mutant RMX complexes were assembled into protein complexes as described previously (9, 13). The concentration of proteins and protein complexes was determined by densitometric scanning of Coomassie Blue-stained 7.5% SDS-PAGE gels (30) that contained different loadings of the proteins and protein complexes with known amounts of bovine serum albumin as the comparison standard.

DNA End-joining Assay—Purified wild-type and mutant RMX complexes (1.2 μM of each) were incubated with 150 μM [γ-32P]ATP and Xrs2 and mutant ATPase activity of the RMX complex as described previously (9). The wild-type and mutant proteins purified by the same procedure devised for wild-type Rad50 (9). Wild-type and mutant Rad50 proteins were assembled into protein complexes as described previously (9, 13). The concentration of ATP hydrolysis was determined by thin layer chromatography (TLC), as described (31).

DNA Substrates—To construct the substrate for the DNA binding experiments, the 5′-end of the 83-mer oligonucleotide: 5′-TTG ATA AGA GGT CAT TTT GTC GGA TGG CTT AGA GCT TAA TTG CTG -3′ was radiolabeled using T4 polynucleotide kinase (Promega) and [γ-32P]ATP (Amersham Biosciences). The polynucleotide kinase was inactivated by heating the substrate mixture to 75 °C for 10 min and unincorporated ATP was removed with a Spin 30 column (Bio-Rad). The labeled oligonucleotide was annealed with its exact complement and the 83-base pair duplex was purified from 10% native polyacrylamide gel by overnight diffusion at 4 °C into TAE buffer (40 mM Tris acetate, pH 7.5, 0.5 mM EDTA). To make topologically relaxed DNA, Xrs2–containing replicative form I DNA (Invitrogen, Life Technologies, Inc.) was treated with calf thymus topoisomerase I (3 units; Invitrogen), followed by purification of the relaxed DNA species from agarose gels containing ethidium bromide, as described (32). The relaxed DNA was stored in TAE buffer.

Topological DNA Unwinding Assay—Wild type and mutant RMX complexes (1 μM of each) were incubated with topologically relaxed X174 replicative form I DNA (Invitrogen) at 37 °C in 10 mM Tris phosphate, 0.5 mM MgCl2, and 32P-labeled molecules detected by phosphorimaging analysis.

Endonuclease Assay—The DNA hairpin (HP2) with ssDNA overhangs was labeled at the 3′-end as described previously (9). This substrate (120 nt nucleotides) was incubated with 400 nt of the wild-type and mutant RMX complexes at 4 °C in 10 μl of Buffer A containing 1 mM ATP and 5 mM MnCl2 instead of MgCl2. After 40 min at 37 °C, the reaction was halted by the addition of SDS and proteinase K (0.2% and 0.5 mg/ml, respectively). After separation by denaturing polyacrylamide gel electrophoresis, radiolabeled DNA species were detected in the dried gel by phosphorimaging analysis (9).

Exonuclease Assay—A 3′-end-labeled 74-nt duplex DNA substrate was generated by the hybridization of complementary oligonucleotides as described previously (9). This duplex (7.4 μM nucleotides) was incubated with 400 nt of the wild-type and mutant RMX complexes at 4 °C in 10 μl of Buffer A that contained 5 mM MnCl2 instead of MgCl2. At the times indicated, an aliquot (2 μl) was removed and deproteinized by incubation with SDS (0.2%) and proteinase K (0.5 mg/ml) for 10 min at room temperature. After separation by TLC, the plates were air-dried and 32P-labeled molecules detected by phosphorimaging analysis.

In Vitro DNA End-joining Assay—Linear 400-nt DNA fragments with either 5′ or 3′ complementary single-stranded ends were gener-
Mutation of the Rad50 Walker A motif sensitizes *S. cerevisiae* cells to ionizing radiation and methyl methanesulfonate; complementation of DNA damage sensitivity by overexpression of ExoI. A. sensitivity of rad50 mutant strains to ionizing radiation as a function of the radiation dosage. B. aliquots of 10-fold serial dilutions of cultures of yeast strains were spotted onto YPD plates and either exposed to ionizing radiation (200 Gy, right panels) or not (left panels). The strains in the two lower panels harbored a plasmid encoding either the RAD50 or XRS2 gene under the control of the *ADH* promoter, as indicated. C. aliquots of 5-fold serial dilutions of yeast cultures were spotted onto yeast synthetic media plates lacking glutamine and leucine either without (left panel) or with (right panel) 0.3 mM methyl methanesulfonate (MMS). The strains either harbored the empty vector (Vector) or the vector expressing ExoI from the *ADH* promoter (ADHp:EXO1) as indicated.

RESULTS

Mutations in the Walker A Motif of Rad50 Cause Hypersensitivity to DNA-damaging Agents—Rad50 protein is a DNA-dependent ATPase (9) and binds DNA in an ATP-dependent manner (18). To elucidate how ATP regulates the functions of Rad50 and the RMX complex, we changed the conserved lysine residue (Lys40) in the Walker A motif of Rad50 to arginine (K40R), alanine (K40A), and glutamic acid (K40E) by site-directed mutagenesis. Yeast strains in which the RAD50 gene was replaced by the three mutant alleles were as sensitive as the isogenic rad50Δ strain to killing by ionizing radiation (IR) (Fig. 1A) and by methyl methanesulfonate (Fig. 1C). As expected, the DNA damage sensitivity of the rad50 mutants was fully complemented by the wild-type RAD50 gene but not the XRS2 gene (Fig. 1B). By contrast, replacement of the RAD50 gene with the rad50Δ allele (K11), which is defective in the removal of Spo11 from DNA double strand breaks during meiosis (34), did not confer increased sensitivity to DNA damage (data not shown). Recently, it was shown that overexpression of ExoI, a 5'- to 3'- exonuclease (35), suppressed the DNA damage hypersensitivity of rad50Δ, mre11Δ, and xrs2Δ strains (12). Overexpression of ExoI also suppressed the DNA damage hypersensitivity of rad50Δ, rad50Δ mre11Δ, and rad50Δ xrs2Δ strains although not quite to the same extent as the rad50Δ strain (Fig. 1C), suggesting that the presence of a defective Rad50-Mre11-Xrs2 complex may hinder ExoI activity. rad50 Walker A Mutants Are Compromised for Recombination DNA Repair—Since inactivation of NHEJ in *Saccharomyces cerevisiae* does not cause an appreciable increase in
sensitivity to ionizing radiation, it appears that defects in recombination repair mechanisms underlie the hypersensitivity of rad50 strains (1, 26, 36). Based on the survival curves of the rad50 Walker mutant strains, we predicted that these strains would also be defective in homologous recombination. To test this idea, we used an assay that measures homologous integration of a linearized plasmid molecule (12). As anticipated, the rad50 K40A, rad50 K40R, and rad50 K40E mutants exhibited a marked defect in plasmid integration similar to that of the rad50Δ strain (Fig. 2A). In contrast, the rad50S strain was only slightly impaired (data not shown).

**Rad50 Walker A Mutants Are Defective in DNA End-joining**—Although inactivation of NHEJ in yeast does not cause a significant increase in sensitivity to DNA damaging agents, defects in this pathway do result in a reduced ability to recircularize linearized plasmid DNA molecules (2, 26, 29, 37, 38). Therefore, we asked whether yeast strains harboring mutations in the Rad50 Walker A domain are defective in recircularizing linearized plasmid DNA molecules linearized by digestion with EcoRI. As shown in Fig. 2B, the three rad50 Walker mutations impair plasmid rejoicing, although not to the same extent as the rad50Δ mutation.

**The Rad50 Walker Mutant Proteins Are Deficient in Complex Assembly and Defective in ATP Hydrolysis**—The K40R, K40A, and K40E variants of Rad50 were overexpressed in yeast and purified to near homogeneity (Fig. 3A) using the purification scheme previously devised for wild-type Rad50 protein (9). No significant difference in either the extent of overexpression or in chromatographic behavior was observed for the mutant Rad50 proteins (data not shown). To assemble protein complexes, purified wild-type Rad50, and the three Walker A mutants were incubated with purified Mre11 and Xrs2, and the resulting complexes were separated from unassembled proteins by gel filtration (13). The yield and relative stoichiometry of the complexes formed with the mutant variants of Rad50 were very similar to those containing wild-type Rad50 (Fig. 3B), indicating that the Walker mutations in Rad50 do not affect complex formation with Mre11 and Xrs2.

The ATPase activity of Rad50 requires complex formation with Mre11 for its full expression, whereas Xrs2 has no discernable effect in this regard (10). As shown in Fig. 4, RMX complexes containing either Rad50 K40A or Rad50 K40E are essentially devoid of ATPase activity. Although the Rad50 K40R complex has detectable ATPase activity, it is markedly reduced compared with the wild-type complex (Fig. 4). This suggests that, as has been observed with other proteins containing a Walker A motif, replacement of the lysine residue with arginine does not abolish ATP binding but greatly attenuates hydrolysis (39, 40).

**The Rad50 Walker Mutant Proteins Are Unresponsive to ATP in DNA Binding and Unwinding Reactions**—Previous studies have shown that binding to double-stranded DNA by Rad50 protein is dependent on ATP (15, 18). To examine the DNA binding properties of the Rad50 Walker mutant proteins, we incubated wild-type Rad50, and the mutant proteins with a radiolabeled DNA substrate either in the presence or absence of ATP. As expected, wild-type Rad50 bound the DNA substrate in an ATP-dependent manner, whereas the mutant versions of Rad50 failed to form a complex with the substrate with or without ATP (Fig. 5).

The RMX complex alters the topology of DNA in an ATP-dependent reaction (10). This activity can be studied by incubating the RMX complex with topologically relaxed DNA, ATP, and calf thymus topoisomerase I to generate a negatively supercoiled DNA product referred to as Form U (10). As shown in Fig. 6, none of the mutant RMX complexes was capable of generating Form U DNA, indicative of a requirement for the Rad50 ATPase activity in DNA unwinding.

**Effect of the rad50 Walker Mutations on the Nuclease Activities of the RMX Complex**—We next assayed the wild type and mutant variants of the RMX complex for DNA structure-specific endonuclease activity using a hairpin substrate that contains two single-stranded overhangs (9). The RMX complex makes two endonuclease incisions in this substrate, with one of the incisions occurring at the tip of the hairpin to generate product A, and the other at the junction between the 3′ single-strand overhang and the duplex to yield product B (Fig. 7A). In accord with published studies (10), the endonuclease activity of the wild-type complex was markedly enhanced by ATP. By contrast, the endonuclease activity of the mutant complexes, which was similar to that of the wild-type complex in the absence of ATP (Fig. 7A), was not stimulated by ATP. Taken together, we concluded that the ATP-dependent stimulation of the DNA structure-specific endonuclease of the RMX complex is contingent upon ATP hydrolysis. Unlike the endonuclease activity, ATP does not affect the exonuclease activity of the Rad50-Mre11 complex significantly (9). Congruent with this
observation, the exonuclease activity of RMX complexes containing the mutant variants of Rad50 was similar to that of the wild-type complex (Fig. 7B).

ATP Is Not Required for the Stimulation of Dnl4-catalyzed Intermolecular Ligation by RMX—As has been observed for purified mammalian DNA ligase IV (41), a significant fraction of Dnl4 (50–60%) in purified preparations of the Dnl4-Lif1 complex is preadenylated (data not shown). This allowed us to examine the effect of ATP on the ability of the RMX complex to promote Dnl4-catalyzed intermolecular ligation (13). Interestingly, the stimulation of intermolecular ligation was independent of ATP during the initial phase of the reaction. Only after incubation for 60 min was there a small increase in the fraction of Dnl4-Lif1 complex that remained as monomer following incubation with the wild-type RMX complex either at 15 mM KCl (Fig. 8A), or 100 mM KCl (Fig. 8B). The mutant complex that contained Rad50 K40R showed robust end-bridging activity at 15 mM KCl, linking greater than 80% of the DNA molecules (Fig. 8B, lanes 4 and 7), whereas at 100 mM KCl, the end-bridging activity was significantly inhibited with greater than 70% of the molecules remaining as monomers. Taken together, our biochemical results indicate that amino acid substitutions in the Walker A box of Rad50 (Fig. 2B) are sufficient to cause a conditional defect in DNA end-bridging and DNA end-joining that is revealed by the inclusion of a physiological level of salt.

**DISCUSSION**

The evolutionarily conserved RMX complex plays a complex and multifaceted role in the cellular response to DNA damage

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**Fig. 5. DNA binding by wild type and mutant variants of Rad50.** 
32P-labeled 83-mer duplex substrate was incubated with WT Rad50 and its mutant (K40A, K40E, and K40R) variants in the presence or absence of ATP, as indicated. The protein amounts were 130 nM (lanes 2 and 5), 185 nM (lanes 3 and 6), and 230 nM (lanes 4 and 7). After separation by native polyacrylamide gel electrophoresis, labeled DNA species were detected by phosphorimaging analysis of the dried gel. No protein was added to the reaction mixture in lane 1, and in lane 8, the reaction mixture containing 230 nM protein was deproteinized with SDS and proteinase K (PK) prior to analysis.

**Fig. 6. Effect of the rad50 Walker mutations on the ATP-dependent DNA unwinding activity of the RMX complex.** 
RMX complexes containing the WT and mutant (K40A, K40E, and K40R) variants of Rad50 were incubated with topologically relaxed dX174 DNA and calf thymus topoisomerase I in the presence of ATP. No protein was added to the reaction mixture in lane 1, and in lane 3, ATP was omitted from the reaction mixture containing the wild-type RMX complex. After deproteinization, the reaction mixtures were resolved by agarose gel electrophoresis, and the DNA species were stained with ethidium bromide. In the presence of ATP, the wild-type RMX complex generates a negatively supercoiled or underwound DNA species (Form U) that migrates faster than relaxed (Relaxed) DNA.
and the maintenance of genome stability in eukaryotes (1, 42, 43). At the biochemical level, this complex has DNA binding, DNA unwinding, nuclease, and ATPase activities (8–10, 18, 19, 44), and it interacts with several proteins involved in the DNA damage response (13, 20, 21, 23, 24). Here we have examined the role of ATP binding and hydrolysis by the Rad50 subunit on the biochemical properties and cellular functions of the RMX complex, in particular the repair of DSBs.

Based on genetic studies, it appears that the DNA damage sensitivity of rad50 strains is predominantly caused by a defect in the recombinational repair of DSBs and that the RMX complex acts at an early stage in this repair pathway (1, 22, 45). Strains harboring mutant variants of RAD50 with amino acid substitutions of the conserved lysine residue within the Walker A motif exhibit the same hypersensitivity to DNA damaging agents and defect in mitotic recombination as the rad50/H9004 mutant. Importantly, these amino acid substitutions do not disrupt complex formation with Xrs2 and Mre11 but, as expected, they inactivate ATP hydrolysis by the RMX complex and other ATP-modulated functions of this complex, including the DNA unwinding and DNA structure-specific endonuclease activities.

The rad50 K40E allele was shown previously to be defective in meiotic DSB formation (46). In a recent study, Moncalian et al. (47) mutated a different region of the Rad50 ATP binding site and reached a similar conclusion regarding the critical role of ATP hydrolysis by Rad50 in homologous recombination. The notion that the role of the RMX complex in the recombinational repair of damaged DNA is to generate a single-stranded DNA substrate via its ATP-stimulated nuclease function is supported by the observation that the DNA damage sensitivity of rad50 strains can be suppressed by ExoI overexpression (12). Although the RMX complex is a core factor in the pathway that repairs DSBs by NHEJ, the majority of end-joining events do not involve extensive nucleolytic resection from the break site (1, 26, 36). Indeed, the recircularization of linear plasmid DNA molecules with complementary ends occurs efficiently in yeast strains lacking the Mre11 nuclease activity (5). Thus, the ATP-stimulated endonuclease function of the RMX complex is largely dispensable for DSB repair by NHEJ. Based on bio-

**FIG. 7.** Effect of the rad50 Walker mutations on the endonuclease and exonuclease activities of the RMX complex. A, RMX complexes containing the WT and mutant (K40R, K40A, and K40E) variants of Rad50 were incubated with the oligonucleotide-based hairpin substrate (HP2) in the presence or absence of ATP, as indicated. After separation by denaturing polyacrylamide gel electrophoresis, labeled DNA species were detected in the dried gel by phosphorimaging analysis. The positions of products corresponding to hairpin cleavage (A), cleavage of the 3’ single strand end (B), and exonuclease activity (AMP*) are indicated. B, RMX complexes containing the WT and mutant (K40R, K40A, and K40E) variants of Rad50 were incubated with a 3’-end-labeled DNA duplex. At the times indicated, aliquots were removed, deproteinized, and analyzed by TLC. The TLC plate was air-dried and the labeled substrate (Duplex*) and nucleoside monophosphate (NMP*) product were revealed by phosphorimaging analysis. The data are shown graphically in the lower panel.

**FIG. 8.** The mutant Rad50 proteins have a conditional deficiency in DNA end-joining. A, radiolabeled 400 bp DNA substrate with 5’-cohesive ends was incubated with Dnl4/Lif1 and, where indicated, RMX and ATP. Aliquots were taken after 15 and 60 min of incubation, deproteinized, and analyzed. B, Dnl4-catalyzed end-joining was carried out at either 10 mM (left panel) or 100 mM (right panel) KCl. RMX complexes containing the WT and mutant (K40A, K40E, and K40R) variants of Rad50 were added as indicated. The radiolabeled DNA species were revealed by phosphorimaging analysis of dried agarose gels. The positions of the linear substrate, linear dimer, and linear trimer are indicated. The arrow indicates higher oligomers.
chemical studies, it appears that one of the critical functions of the RMX complex in NHEJ is to engage DNA ends and juxtapose them (13). Although DNA binding by Rad50 is ATP-dependent (18), our studies have shown that the DNA end-bridging activity of RMX is not (10, 13). Given these observations, the significant defect in NHEJ exhibited by strains harboring the rad50 Walker mutations was surprising. In subsequent studies, we demonstrated that the ability of the wild-type and mutant RMX complexes to perform DNA end-bridging and to promote intermolecular ligation by adenylated Dnl4/Lif1 is ATP-independent. However, under more stringent reaction conditions that more closely resemble the physiological situation, the mutant complexes are clearly deficient in DNA end-bridging and stimulating intermolecular ligation by Dnl4/Lif1.

These biochemical results provide a molecular explanation for the observed defect in NHEJ conferred by the rad50 Walker mutations and also evidence for a novel ATP-independent function for the Rad50 Walker A motif in DNA end-bridging and NHEJ.

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