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MutL associates with *Escherichia coli* RecA and inhibits its ATPase activity

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ABSTRACT

Different DNA repair systems are known to cooperate to deal with DNA damage. However, the regulatory role of the cross-talk between these pathways is unclear. Here, we have shown that MutL, an essential component of mismatch repair, is a RecA-interacting protein, and that its highly conserved N-terminal domain is sufficient for this interaction. Surface plasmon resonance and capillary electrophoresis analyses revealed that MutL has little effect on RecA–ssDNA filament formation, but dose down-regulate the ATPase activity of RecA. Our findings identify a new role for MutL, and suggest its regulatory role in homologous recombination.

Introduction

Living organisms are continuously exposed to damaging agents from both internal and external environments. Cells have therefore evolved several repair systems to counteract potential threats to the stability of DNA and allow the accurate transmission of genetic information [1]. One such repair system is homologous recombination, a high fidelity DNA repair mechanism found in all forms of life that plays a very important role in the repair of double-stranded DNA breaks [2]. The *Escherichia coli* RecA protein plays an essential role in this repair pathway and has been used as a model system for studying DNA strand exchange, the central step of homologous recombination [3,4]. Like archaeal RadA and eukaryotic Rad51, bacterial RecA promotes an ATP-mediated strand exchange reaction by polymerizing on DNA and forming a helical filament [5].

It is well known that there is cross-talk between different DNA repair pathways [6,7]. It has been suggested that there is cross-talk between homologous recombination and the mismatch repair system, since recombination between highly diverged sequences is differentially inhibited by the mismatch repair system [8,9]. MutL, a mismatch repair protein with DNA binding and ATPase activity, has also been reported to enhance MutS's inhibition of RecA-mediated homologous strand exchange between sequences which differ by 3% at the nucleotide level [10]. In mammalian cells, hMLH1, the homolog of MutL, also appears to monitor homologous recombination independent of mismatch repair [6]. However, the mechanism underlying the cross-talk between homologous recombination and the mismatch repair system, and in particular how MutL exerts its effect on homologous strand exchange, is unclear.

Here we show that there is a physical interaction between MutL and the recombinase protein RecA, and that the highly conserved N-terminal domain of MutL is essential for this interaction. MutL down-regulates RecA ATPase activity, but does not affect RecA–ssDNA filament formation. Our results support the hypothesis that MutL may play a regulatory function in homologous recombination through its interaction with RecA.

Materials and methods

Protein purification

All strains were grown routinely in Luria–Bertani (LB) media. Antibiotics were added when required at the following concentrations: ampicillin, 100 μg/ml; kanamycin, 60 μg/ml.

The *mutL* gene and its derivative mutants were cloned from *E. coli* strain MG1655. The gene was amplified by PCR, cloned into a pQE-30 vector, and transformed into the BL21 (DE3) strain. Histidine-tagged MutL, LN40 (residues 1–349), LC20 (residues 439–615), L-E29A, L-R266E, RecA and RecA–SBP (with a streptavidin-binding peptide inserted into the C-terminus of the *recA* gene) proteins were purified using a Ni-chelating affinity column [11]. Proteins were further purified by size-exclusion chromatography and were shown to be at least 90% pure by Coomassie staining after SDS polyacrylamide gel electrophoresis. Fractions were dialyzed in

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20 mM Tris–HCl (pH 7.8) containing 200 mM NaCl, 1 mM DTT, 0.5 mM EDTA, and 10% glycerol, and concentrated to ~6 mg/ml. The RecA protein was also partly dialyzed in PBS buffer (pH 7.4) before SPR[1] analysis. All these proteins were stored at −80 °C.

To couple a glutathione-S-transferase tag to RecA, the *recA* gene was ligated into the pGEX6p-1 vector using its BamHI and XhoI restriction sites. Expression was induced with 0.1 mM isopropyl-1-thio-β-D-galactopyranoside overnight at 16 °C. Bacterial cultures were harvested and pellets were resuspended in PBS. Purification of GST-tagged proteins was performed with glutathione resin (Sigma, USA). The resin was washed with PBS and the purity and amount of bound GST protein was determined by SDS–PAGE and Coomassie blue staining. Single strand binding protein (SSB) was purchased from Promega (USA).

DNA substrates

Single-stranded DNA, M13mp18, was prepared as described by Lu et al. [12]. Single-stranded 90mer-polyT oligodeoxynucleotides labeled at their 5′-terminals by the fluorescent dye tetramethylrhodamine (TMR), used for highly sensitive laser-induced fluorescence detection, were dissolved in 20 mM Tris–HCl (pH 7.4), 10 mM Mg^{2+} and purified by high performance liquid chromatography (HPLC) [13]. The 5′-biotinylated single-stranded 90mer-polyT used in SPR analysis was dissolved in 20 mM Tris–HCl (pH 7.8), containing 10 mM Mg^{2+} and 50 mM NaCl.

Far-Western blotting

MutL-LC20, MutL-LN40, MutL-E29A, MutL-R266E, MutL and BSA, at the concentrations indicated (0.125–2 μM), were spotted onto Protran nitrocellulose membranes (Whatman). Membranes were blocked in blocking buffer (3% defatted milk, 0.05% Tween 20, PBS) at room temperature for 1 h and then incubated with 5 μM SBP-tagged RecA in the same buffer overnight at 4 °C. After washing, membranes were incubated with streptavidin alkaline phosphatase (Promega, USA) at room temperature for 1 h, washed again, and then developed using BCIP-NBT solution (Amresco, USA) [14]. Results were recorded using an Epson Perfection 2580 PHOTO scanner (Epson, Japan).

In vitro pull-down assays

Hundred ng GST-tagged RecA bound to glutathione beads was centrifuged at 500*g* for 5 min and then washed three times with 1 ml PBS containing 1% Triton X-100. His-tagged MutL and its derivative mutants were added to the GST-tagged RecA immobilized on glutathione–Sepharose 4B (Sigma, USA) and incubated for 1 h in 500 μl binding buffer (25 mM Tris–HCl, pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, 10% glycerol, 1% Triton X-100, 0.5 mM DTT, 1% BSA) at 4 °C. After centrifugation at 500*g* for 5 min, the pellets were washed five times with 500 μl binding buffer at 4 °C and fractionated on a 10% SDS polyacrylamide gel [15]. Western blotting of His-tagged MutL and its derivative mutants was carried out with a primary antibody specific to polyHistidine (Monoclonal Anti-polyHistidine, Sigma, USA) and an anti-mouse-HRP conjugate (HRP-linked Anti-Mouse IgG, Sigma, USA) as a secondary antibody.

Surface plasmon resonance

SPR experiments were carried out on a BIAcore 3000 machine (BIAcore AB, Uppsala, Sweden) at 25 °C. To ensure the interaction between RecA and MutL, a carboxymethylated dextran surface-modified chip (CM5 chip) was used. The RecA sensor chip was prepared according to the amine-coupling protocol in the BIAcore manual. Proteins were diluted in PBS running buffer. The streptavidin-modified chip (SA chip) was also used to measure DNA–protein binding activity. Before immobilizing the 20 nM 5′-biotinylated 90mer-polyT, the SA chip was activated by three consecutive injections of 1 M NaCl plus 50 mM NaOH. The proteins were diluted in running buffer (20 mM Tris–HCl, pH 7.8, 10 mM Mg^{2+} and 50 mM NaCl). Samples were injected at different concentrations at a flow rate of 30 μl/min. Regeneration of the sensor chip surface was achieved by a quick injection of 0.1% SDS in buffer. All SPR data were evaluated using BIA evaluation software (from BIAcore).

Capillary electrophoresis for detecting ssDNA binding activity

A helium–neon green laser (543.5 nm, 1 mW, Melles Griot, Irvine, CA) was used as the excitation light source in the CE system. The emitted fluorescence of the analyte was split into vertically and horizontally polarized fluorescence by a polarizing beam splitter (Melles Griot, Nepean, Canada) and detected separately at 575 nm with two photomultiplier tubes (PMT, model R3896, Hamamatsu Photonics, Japan). Data were acquired at a frequency of 20 Hz and handled with an HW-2000 chromatographic workstation [13].

The RecA protein and 5 nM TMR-90mer-polyT ssDNA were incubated at 37 °C in 1× TH-Mg^{2+} buffer (20 mM Tris–HCl, 10 mM Mg^{2+}, pH 7.4) just before the addition of MutL or L-R266E. The samples were electrokinetically injected into an uncoated fused-silica capillary by applying an electric field of 500 V/cm for 5 s. The separation was carried out by applying an electric field of 466 V/cm in 1× TG buffer (25 mM Tris, pH 8.3, 192 mM glycine).

ATPase assays

ATPase activity was assayed at 37 °C and monitored in a U-2010 spectrophotometer (Hitachi, Japan). Regeneration of ATP from ADP in the presence of phosphoenolpyruvate (PEP) was coupled to the oxidation of NADH, and the decrease in NADH concentration was followed at 340 nm. The extinction coefficient of NADH (1.21 $mM^{-1}\,cm^{-1}$) at 340 nm was used to calculate the amount of ATP hydrolyzed [16].

Reactions contained 25 mM Tris-Oac (pH 7.4), 1 mM DTT, 3.5 mM potassium glutamate, 3 mM magnesium acetate, 5% glycerol, an ATP regeneration system (10 U/ml pyruvate kinase and 1.75 mM PEP), a coupling system (1.5 mM NADH and 10 U/ml lactate dehydrogenase), and superfluous 1 nM M13mp18 ssDNA [17], and modulator proteins were added just after the addition of RecA. After incubation with 1.2 μM RecA for 10 min, 0.2 μM SSB and 3 mM ATP were added to initiate the reaction. The change in absorbance was related to ADP production using $A_{340}^{1mM} = 6.22\ cm^{-1}$ with NAD^+ production being stoichiometric to the amount of ADP released [18].

Results

RecA interacts directly with MutL through its N-terminal

To investigate the interaction between RecA and MutL, we first determined whether their association is direct using Far-Western blotting. We expressed a series of MutL and its derivative mutants in *E. coli* and performed the Far-Western blotting assay using BSA as a negative control. As shown in Fig. 1A (left panel), the 40 kDa highly conserved N-terminal fragment of *E. coli* MutL, LN40 (residues 1–349) [19], was able to interact directly with RecA (lane 2), to a similar extent as MutL (lane 4). However, when LC20 (C-terminal fragment, residues 439–615), the MutL N-terminal

[1] *Abbreviations used:* SBP, streptavidin-binding peptide; GST, glutathione-S-transferase; BCIP-NBT, 5-bromo-4-chloro-3-indolylphosphate-nitroblue tetrazolium; SPR, surface plasmon resonance; CE, capillary electrophoresis.

deletion mutant was used, no interaction was detected (Fig. 1A left panel lane 1). These observations indicate that the N-terminal of MutL is necessary for the interaction. Pull-down assays using full-length and truncated MutL proteins with GST-fused RecA confirmed the association between the N-terminal of MutL and RecA *in vitro*. As shown in Fig. 1B, MutL and LN40 could be pulled down by RecA, while LC20 did not bind to GST-RecA (Fig. 1B upper right panel). From these results, we conclude that MutL interacts with RecA directly and that the N-terminal of MutL is essential and sufficient for the interaction.

Using Far-Western blotting and pull-down assays, we then determined whether the MutL N-terminal mutants, L-R266E and L-E29A, which are deficient in MutL's DNA binding activity [20] and ATPase activity [21], respectively, were able to interact with RecA. Results demonstrated that both mutants are able to interact strongly with RecA (Fig. 1A and B lower right panel), suggesting that residues 266 and 29 do not disrupt the interaction with RecA, and that these mutants can be used as tools for excluding the possibility that the DNA binding or ATPase activity of MutL influences its regulation of RecA.

MutL has no effect on RecA filament formation

Given that MutL interacts with RecA (Fig. 1), we investigated whether this interaction has any effect on the function of RecA. We assessed the effect of MutL on the polymerization of RecA on ssDNA using SPR and CE. We first confirmed that SPR could detect interactions between MutL and RecA (Fig. S1) and then used it to measure the binding of MutL to RecA in complex with ssDNA. We detected a strong signal (1800 RU) when 1 μM RecA was injected onto a SA chip with immobilized single-stranded biotinylated 90mer-polyT (20 nM), indicating strong binding of RecA to the ssDNA. MutL was then injected at different concentrations (0.5–2 μM) after equilibrium binding of RecA to ssDNA had been reached. There was hardly any increase in the signal detected (Fig. 2B), suggesting that MutL does not interact with the RecA–ssDNA complex. To exclude the possibility that the signal did not change because MutL bound to the ssDNA in place of RecA, the MutL mutant R266E which is deficient in ssDNA binding [20] (Fig. 2C) but can interact with RecA (Fig. 1) was used. Injection of R266E (1 μM) similarly did not result in an increase in the signal (Fig. 2D), confirming that MutL does not interact with the RecA–polyT complex.

The effect of MutL on the RecA–ssDNA complex was investigated further by CE. Compared with ssDNA alone as a negative control (Fig. 3A black line), the amount of unbound 90mer-polyT decreased after the addition of RecA, and an additional fluorescent signal appeared at 2.5 min, indicating formation of a RecA–ssDNA complex (Fig. 3A red line). To explore the effect of MutL on the RecA–ssDNA complex, the protein MutL which measured with higher 90mer-polyT affinity (Supplementary Table S1) was added just after the incubation of RecA and ssDNA. The amount of free

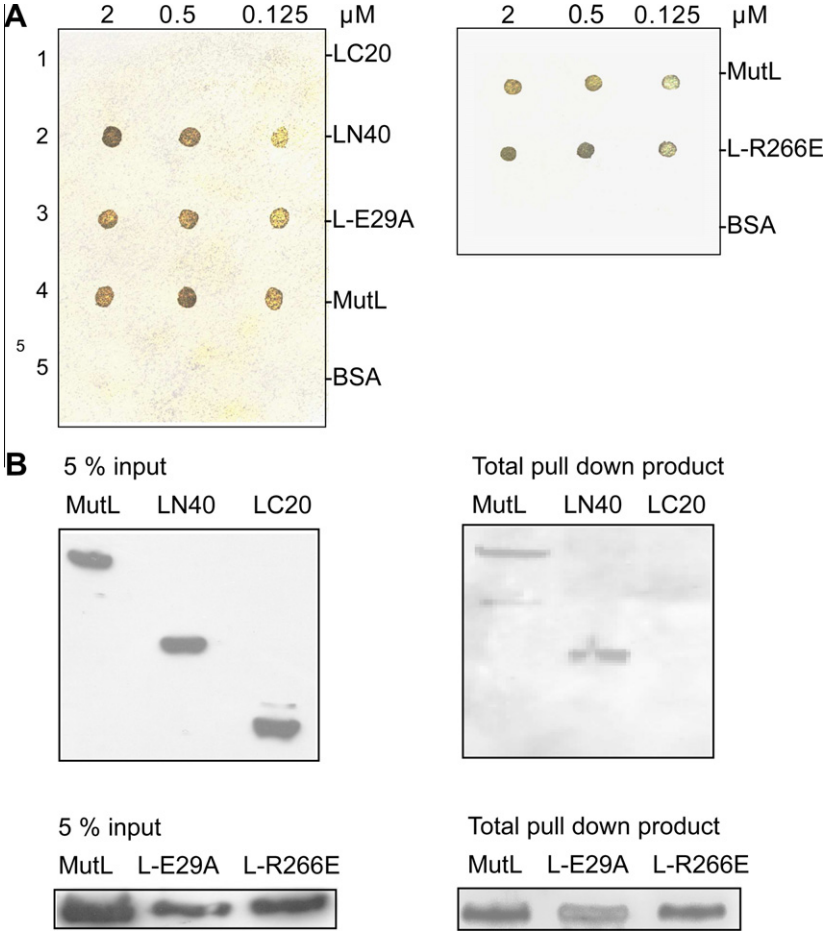

Fig. 1. The MutL N-terminal associates with RecA. (A) Far-Western blot of MutL and RecA. MutL and its mutants were spotted on nitrocellulose membranes (Whatman), which were then incubated in 5 μM SBP-tagged RecA for 2 h. SBP–RecA that remained bound to the filter was detected as described in the Materials and methods. BSA was used as a negative control. (B) GST pull-down of MutL and RecA. In the left panel, 5% of the lysate was used as a loading control. Equal amounts of GST-tagged RecA were incubated with purified His-tagged MutL and its mutants (100 ng). The proteins were subjected to Western blotting and probed with a His-tag antibody.

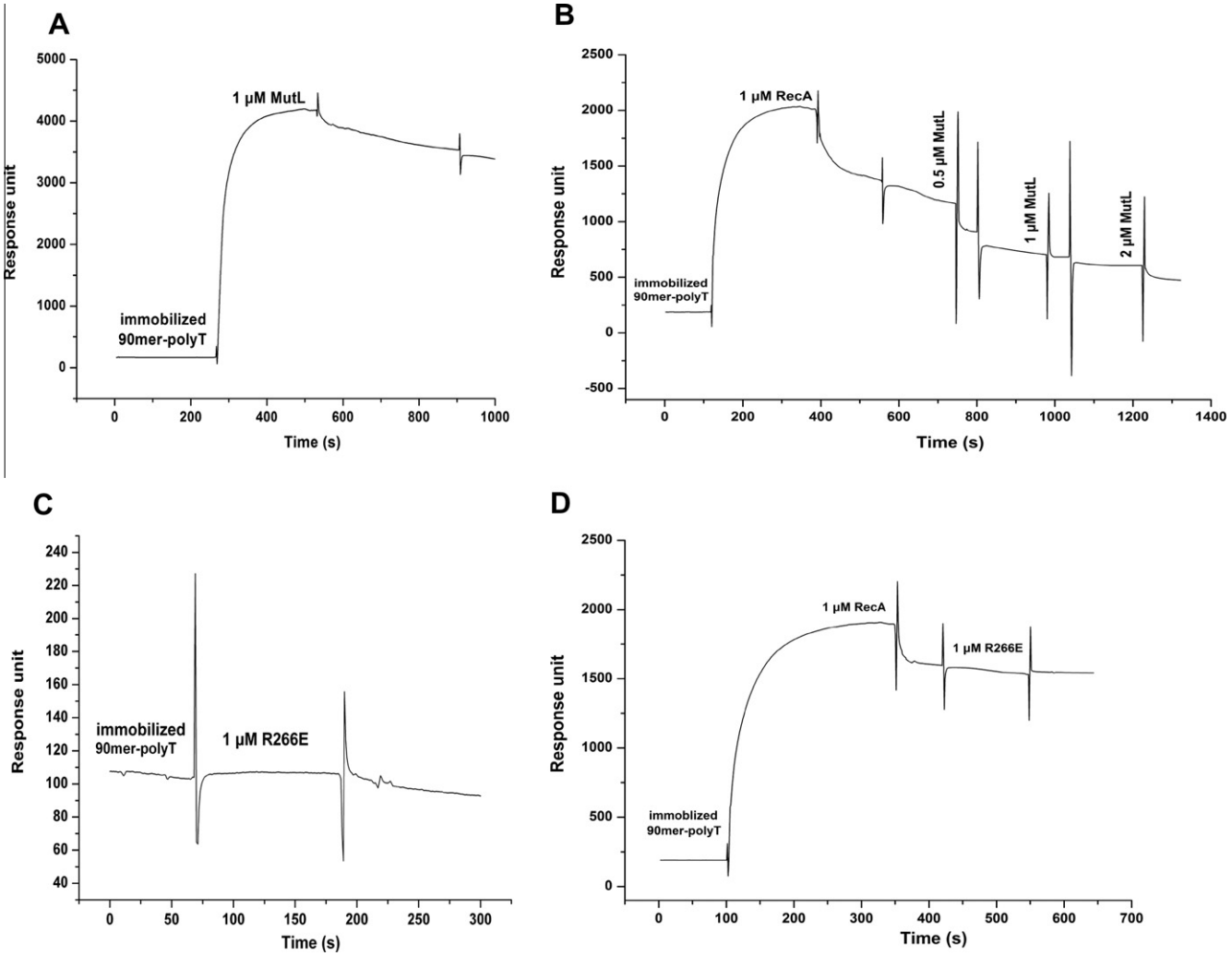

Fig. 2. MutL does not bind the RecA–ssDNA complex. (A) Twenty nanometers 5′-biotinylated 90mer-polyT (172 RU) was immobilized on the SA chip, and 1 μM MutL was injected at 30 μl/min. (B) Twenty nanometers 5′-biotinylated 90mer-polyT (182 RU) was first immobilized on the SA chip, then 1 μM RecA was injected to bind the ssDNA. Increasing concentrations of MutL protein (as indicated) were then injected. (C) Twenty nanometers 5′-biotinylated 90mer-polyT (108 RU) was immobilized on the SA chip, and then 1 μM R266E was injected at 30 μl/min. (D) Twenty nanometers 5′-biotinylated 90mer-polyT (176 RU) was immobilized on the SA chip, then 1 μM RecA was injected to bind the ssDNA. 1 μM R266E was then injected at 30 μl/min. All experiments were repeated at least three times.

ssDNA decreased after the addition of MutL without any influence on the RecA–ssDNA complex. Results indicated that addition of MutL into the system did not have any apparent effects on RecA binding to ssDNA (Fig. 3A blue line). Since MutL alone can bind ssDNA (Fig. 2A) [22] and the fluorescence decreased when MutL alone was added to ssDNA (Fig. S2), we tested the effect of the MutL mutant R266E, which abolishes DNA binding activity (Fig. 2C) [20] but still physically interacts with RecA (Fig. 1) on RecA binding to ssDNA. We detected scarcely any change in the RecA–ssDNA complex formation fluorescent signal and migration time after the addition of different concentrations of L-R266E (Fig. 3B). These results confirm that MutL does not bind to the RecA–ssDNA complex and indicate that MutL has no effect on RecA–ssDNA filament formation.

MutL inhibits the ATPase activity of RecA

As RecA has ssDNA-dependent ATPase activity [23] and MutL has no significant effect on the formation of the RecA–ssDNA complex (Figs. 2 and 3), we wondered whether the interaction between MutL and RecA affects RecA's ATPase activity. By using an ATPase assay that has been used to detect proteins involved in regulating RecA ssDNA-dependent ATPase activity [16,24], we found that after the addition of native MutL to the reaction, the quantity of hydrolyzed ATP decreased; the concentration of hydrolyzed ATP in the MutL/RecA reaction mixture at 50 min (1.2 mM) was lower than either of the two proteins alone (Fig. 4A), suggesting that the ATPase activity of at least one of these proteins was inhibited. To verify whether it was the ATPase activity of RecA which was inhibited by MutL, the MutL mutant L-E29A, which is completely inactive in ATP hydrolysis [21] but still has a physical interaction with RecA (Fig. 1) was added to the reaction system (Fig. 4B). As was the case with wild type MutL, L-E29A also had an inhibitory effect on RecA's ATPase activity (Fig. 4B). These results suggest that the ATPase activity of RecA is down-regulated by MutL.

Discussion

DNA repair systems are known to cooperate through protein–protein interactions when there is genome damage [25]. Here, we report for the first time that MutL, a mismatch repair protein with DNA binding and ATPase activity, can interact with RecA of

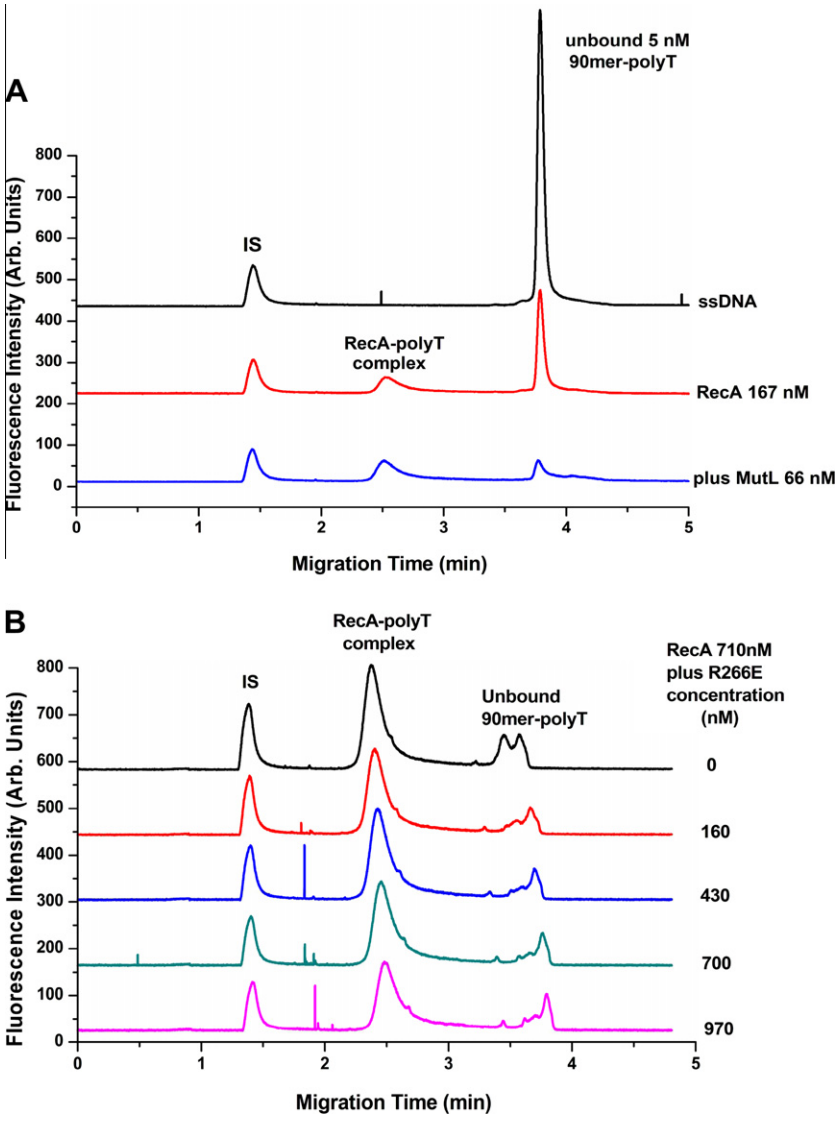

Fig. 3. MutL has no effect on the formation of RecA–ssDNA complexes. (A) 5 nM 5′-TMR 90mer-polyT and RecA protein (167 nM) were incubated in 1× TH-Mg^{2+} buffer. 1× TG buffer, pH 8.3, was used as the running buffer for CE separation. A RecA-90mer-ssDNA complex was detected in the RecA and polyT reaction system at 2.5 min (red), but was not present in the negative control (black). The addition of native MutL had no influence on complex formation (blue). (B) The intensity and migration time of the RecA–ssDNA complex was not influenced by the MutL mutant R266E which was deficient in DNA-binding activity. IS, internal standard. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the homologous recombination pathway via the N-terminal of MutL. Consequently, the ssDNA-dependent ATPase activity of RecA is inhibited by MutL without affecting RecA's DNA binding activity.

The ATPase activity of RecA is important for strand exchange [23] and since DNA is a crucial cofactor of this ATPase, it is dependent on ssDNA binding. Our results show that MutL down-regulates the ATPase activity of RecA (Fig. 4). However, as MutL does not affect RecA–ssDNA complex formation (Figs. 2 and 3), the down-regulation of RecA ATPase activity observed here is probably not related to its ssDNA binding activity. Further research is required to establish the mechanism by which MutL inhibits the ATPase activity of RecA.

In principle, there are three steps in the strand exchange reaction that are experimentally distinguishable: RecA/ssDNA filament formation, homologous sequence alignment and transfer of complementary strands [26]. The ATPase activity of RecA plays a role during its dissociation from ssDNA and in RecA-dependent branch migration in the 5′–3′ direction [23]. In view of the above and our *in vitro* results, we propose that when the ATPase activity of RecA is down-regulated by MutL, the strand exchange which RecA mediates is inhibited without interfering with filament formation, since filament formation does not require ATP hydrolysis [27]. In addition, it has been reported that MutS and MutL alone are unable to inhibit homologous sequence recombination, however, MutL apparently enhances MutS's inhibition of RecA-mediated heterologous sequence exchange [10]. Therefore, we speculate that when MutL binds to heteroduplex-associated MutS in the presence of ATP [28], MutS/MutL dissociation is blocked [29]. The down-regulation of RecA's ATPase activity by MutL is consistent with this since MutL is able to maintain its presence on the heteroduplex through its interaction with RecA (Fig. S3).

When recombination efficiency is evaluated in the *mutL* deficient strain by *in vivo* I-SceI analysis [30], MutL has a negative effect on the repair of DSBs indicating that it interacts with proteins involved in recombination. However, cleavage of the *E. coli* chromosome also induces the SOS response [31]. As RecA promotes not only the strand exchange reaction in bacterial DSB repair [32] but also stimulates LexA cleavage in the SOS response [33], we speculate that the formation of the RecA–MutL complex regulates more than one mechanism.

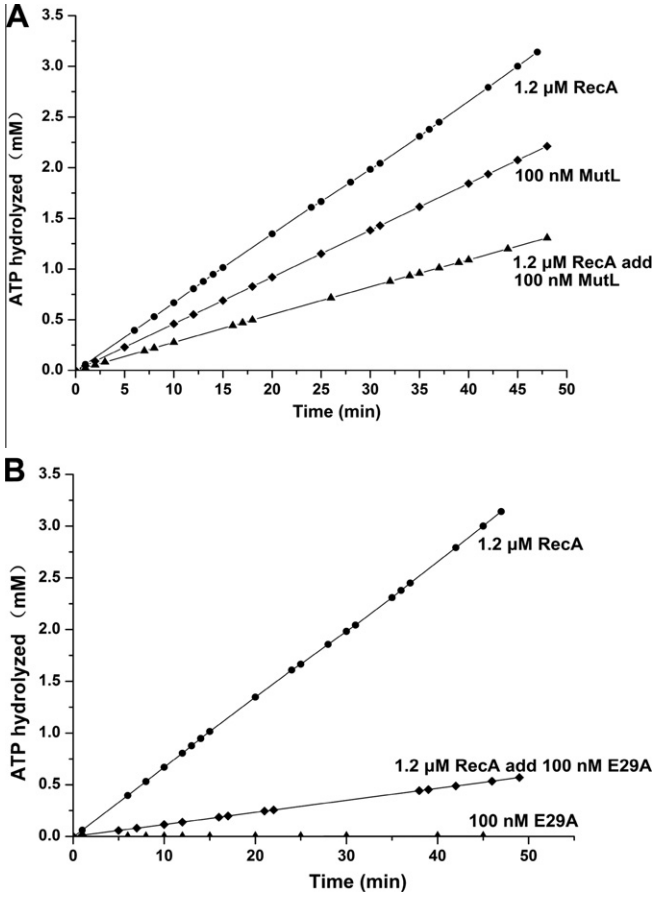

Fig. 4. Effect of MutL variants on RecA ssDNA-dependent ATP hydrolysis. Reactions contained 1.2 μM RecA protein, 2 μM M13mp8 ssDNA, 0.2 μM SSB, and 3 mM ATP. RecA filaments assembled on circular ssDNA hydrolyze ATP at a steady rate. (A) The effect of 100 nM MutL on ATPase activity when added to the reaction after pre-incubation of RecA and ssDNA. (B) The effect of 100 nM E29A on ATPase activity when added to the reaction after pre-incubation of RecA and ssDNA. The MutL ATPase deficient mutant E29A has a marked inhibitory effect. Circle, RecA; diamond, RecA with MutL/E29A; triangle, MutL/E29A.

Our results, based on the cross-talk between the homologous recombination and mismatch repair pathways, together with reports of interactions between MutL and the components of the nucleotide excision repair, base excision repair and very-short-patch repair pathways [7,34], indicate that MutL may not only act as a mismatch repair protein but also a matchmaker in the whole DNA repair architecture.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.abb.2011.09.013.

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