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Functional interaction between MutL and 3′–5′ Exonuclease X in *Escherichia coli*

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ABSTRACT

Exonuclease X is a 3′–5′ distributive exonuclease that functions in DNA recombination and repair. It undergoes multiple rounds of binding, hydrolysis, and release to degrade long substrate molecules and thus is very inefficient. In order to identify a cofactor that elevates the excision activity of ExoX, we screened many proteins involved in repair and recombination. We observed that MutL greatly promoted the exonuclease activity of ExoX, and then verified the interaction between MutL and ExoX using SPR and Far-Western analysis. This promotion is independent of ATP and the DNA-binding activity of MutL. We constructed two deletion mutants to analyze this interaction and its regulation of ExoX activity, and found that this functional interaction with ExoX is mainly due to ionic interactions with the N-terminus of MutL. This adds a new role to MutL and gives a clue to MutL's possible regulation on other DnaQ family exonuclease members.

Introduction

Escherichia coli has multiple exonucleases, many of which play critical roles in modifying DNA substrates created during DNA replication [1,2], recombination [3] and repair [4,5]. There are atleast nine exonucleases in *E. coli* and most of them share redundant roles [6].

Exonuclease X belongs to the DnaQ-like 3′–5′ exonuclease family. Other family members include the bacterial proteins RNase T, RNase D, exonuclease I (ExoI)[1], oligoribonuclease, exonuclease domain of family B DNA polymerases, the *Saccharomyces cerevisiae* PAN2 protein, the human Exonuclease ERI1, Interferon-stimulated gene 20 kDa protein (ISG20), Exosome complex exonuclease RRP6, Three prime repair exonuclease 2 (TREX2) and Werner syndrome protein (WRN) [7]. ExoX has been implicated in UV repair [7], DNA mismatch repair (MMR) [8–10], preventing rearrangements between tandemly repeated DNA sequences [11] and regulating the availability of DNA substrates for recombination [6,12].

ExoX is a distributive exonuclease, capable of degrading both single-stranded and duplex DNA with 3′–5′ polarity. Therefore, unlike processive nucleases, ExoX undergoes multiple rounds of binding, hydrolysis, and release to degrade long substrate molecules [7]. Since this is a very inefficient process, it is likely that this enzyme has a cofactor that elevates its efficiency *in vivo*. We found that MutL greatly promoted the exonuclease activity of ExoX. In *E. coli*, MutL acts as a molecular switch in the whole process of MMR. ATP binding and/or hydrolysis by MutL regulates its interaction with many of the MMR proteins: MutH, UvrD, and the β-clamp of DNA Pol III [13–16]. The DNA-binding activity of MutL affects its own ATP hydrolysis and the stimulation of other MMR proteins, like helicase II and MutH [16]. In addition, MutL could interact with the primary proteins in other DNA repair pathways, including very short patch repair [17,18], nucleotide excision repair [19,20] and base excision repair [21]. It has been suggested that MutL, together with MutS, recruits specialized DNA-modifying enzymes (glycosylases or endonucleases) to lesions that are poorly repaired by MMR [22]. Furthermore, MutL also has a role in inhibiting homeologous recombination [23,24]. The eukaryotic MutL homologues, like the prokaryotic versions, interact with many of the other proteins involved in MMR and other DNA repair pathways. Besides, the eukaryotic MutL homologues also participate in mitosis, meiosis, cell cycle, apoptosis and antibody diversity with its specific roles remains nebulous [22]. There was no report about the interplay between MutL and exonucleases in *E. coli* before. For the first time we found that MutL could elevate the excision activity of ExoX. This regulation points to a novel role of MutL in exonuclease action that may be relevant for regulating MMR and processing double-strand breaks.

Materials and methods

Plasmid construction

Derivatives of the pQE30 plasmid encoding *E. coli exoX* and *mutl* or their mutant genes were constructed. pQE30-*exoX-sbp* and

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[1] *Abbreviations used:* ExoX, Exonuclease X; SBP, streptavidin-binding peptide; SPR, surface plasmon resonance.

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pQE30-*mutL-sbp* were constructed as described previously [14]. Briefly, a streptavidin-binding peptide (SBP,MDEKTTGWRGGHVVE GLAGELEQLRARLEHHPQGQREP) coding sequence and a linker peptide (Ser-Gly-Ser-Gly-Ser-Gly-Ser-Gly-Ser-Gly) coding sequence were inserted together into the C-terminus of the target genes. All clones were confirmed by DNA sequencing.

Protein expression and purification

All proteins were expressed in *E. coli* M15 cultured in Luria–Bertani (LB) medium containing 100 μg/ml ampicillin (Amp) and 35 μg/ml kanamycin (Kan). The cells were cultured at 37 °C. When the absorbance (λ = 600 nm) of the cultures reached 0.6, the cells were induced separately by addition of 0.4 mM isopropyl thio β-D-galactoside (IPTG) in order to express MutL and MutL mutants and cultured at 30 °C for 4 h. The recombinant strain expressing ExoX was induced by IPTG at 16 °C overnight. Cells were harvested by centrifugation at 6000 rpm for 15 min and then lysed by ultrasonication. Cell fragments were separated by centrifugation at 12,000 rpm for 30 min at 4 °C. Proteins were purified using a Ni^{2+}–NTA column (Amersham) and purity was confirmed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE). The MutL and MutL mutants were stored in buffer A (25 mM Tris–HCl (pH 7.6), 500 mM NaCl, 1 mM 1,4-dithiothreitol (DTT) and 10% glycerol). ExoX was kept in buffer A with 50% glycerol.

Far-Western analysis

Protein–protein interactions were identified using a Far-Western assay as described previously [14,25]. The target proteins were loaded separately onto a nitrocellulose membrane at four different concentrations. The SBP-tagged protein was used at a concentration of 800 nM, and tagged protein that remained bound to the filter was detected by incubating the membrane with alkaline-phosphatase conjugated streptavidin (Promega) followed by the alkaline-phosphatase substrate 5-bromo-4-chloro-3-indolyl-phosphate/nitroblue tetrazolium (BCIP/NBT) (DingGuo, Beijing, China). Development of a purple color indicated a positive reaction between the protein loaded on the membrane and the SBP-tagged protein.

SPR experiments

SPR experiments were carried out at 25 °C using a BIAcore 3000 instrument (BIAcore AB, Uppsala, Sweden). To measure the strength of ExoX–dsDNA interactions, 5′ biotinylated DNA was immobilized on a streptavidin (SA)-coated sensor chip at a density that corresponds to 140 response units (RU). A 25 base pair dsDNA substrate was made by annealing oligonucleotide 1 (5′-biotin-CTGGGGAACTTGAACAACTTCGTGC-3′) and oligonucleotide 2 (5′-GCACGAAGTTGTTCAAGTTCCCCAG-3′). To quantify the kinetic parameters of the interactions between ExoX and MutL, 749 RU MutL–SBP was immobilized onto a sensor chip. To measure the strength of the interaction between ExoX and MutL deletion mutants and between ExoX and MutL point mutants, ExoX-SBP protein was immobilized on a SA chip at densities corresponding to approximately 2000 RU and 2500 RU, respectively.

Before measurement, the sensor chip was equilibrated with running buffer (25 mM Tris–HCl (pH 8.0), 125 mM NaCl, 10 mM $MgCl_2$ and 0.005% Tween 20) until the baseline was stable. Running buffer for ExoX–DNA interaction was devoid of $MgCl_2$. Samples were injected at different concentrations at a flow rate of 30 μl/min for 1 min or 2 min. Regeneration of the sensor chip surface was carried out according to the method of Li et al. [26].

The curves were fitted to a 1:1 Langmuir binding model (BIAevaluation 4.1 software) to obtain the equilibrium and kinetic constants.

Exonuclease assays

A 2022 bp dsDNA was used to analyze the excision activity of ExoX. Protein samples were diluted with storing buffer. Standard reaction mixtures (10 μl) contained 10 mM Tris–HCl (pH 8.0), 10 mM $MgCl_2$, 1 mM NaCl, 2 mg/ml BSA, and appropriate amounts of dsDNA substrate, ExoX and MutL or MutL mutants. All the reaction mixtures were incubated at 37 °C for 10 min. Reactions were quenched by the addition of 10 mM EDTA, 0.1% SDS and 150 μg/ml proteinase K and incubated at 42 °C for 30 min. Reaction products were resolved on 0.8% agarose gels, which were stained with ethidium bromide.

Results

MutL physically interacts with Exonuclease X

MutL–SBP retains the bioactivity of MutL [14] and the exonuclease activity of ExoX–SBP was similar to ExoX (SI Fig. 1). Thus, purified MutL–SBP and ExoX–SBP is suitable for investigating potential protein interactions *in vitro*. Far-Western blotting showed that MutL could interact with ExoX (Fig. 1). MutS, known to interact with MutL [27], was used as a positive control, while BSA was used as a negative control. Positive signals were observed in the area of the membrane to which ExoX had bound, indicating that ExoX could interact directly with MutL (Fig. 1a). Positive signals were also observed in the area of the membrane to which MutL had bound (Fig. 1b), confirming the interaction between these two proteins.

In order to validate the newly found interactions and quantify their kinetic parameters, SPR was adopted for further analysis. In

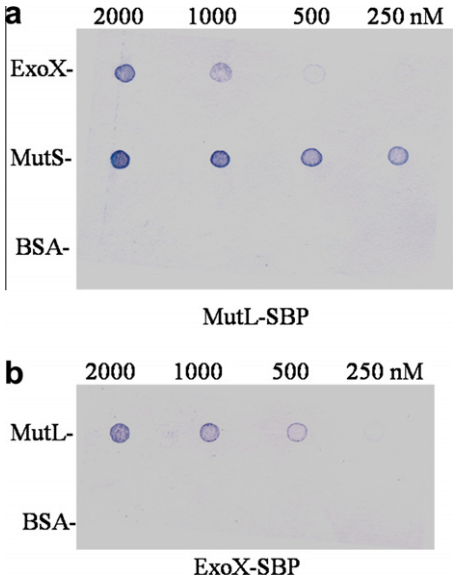

Fig. 1. Far-Western analysis of the interactions between MutL and ExoX. (a) Different concentrations of ExoX, MutS and BSA were applied to a nitrocellulose membrane and then incubated with 800 nM MutL–SBP. MutL–SBP that remained bound to the filter was detected by incubating the membrane with alkaline-phosphatase conjugated streptavidin followed by alkaline-phosphatase substrate as described in the Materials and methods. MutS was used as a positive control and BSA was used as a negative control. (b) The experiments were performed as in (a) except that the indicated concentrations of MutL and BSA were applied to a nitrocellulose membrane and then incubated with 800 nM ExoX–SBP.

this technique, a test protein is passed over a chip containing an immobilized protein. Interactions between the immobilized and test proteins are detected by changes in refractive index [25]. MutL–SBP protein was immobilized on a SA chip at a density corresponding to approximately 749 RU. The stability of the ExoX–MutL complex was determined by injecting solutions containing increasing concentrations of ExoX over the MutL–SBP-immobilized sensor chip.

Response unit (RU) values were proportional to sample concentrations within certain ranges (Fig. 2a). The sensorgram exhibited moderate association and slow dissociation rates. The K_a, K_d, K_A and K_D values of the interactions between MutL and ExoX (Table 1) indicate that MutL had a strong affinity for ExoX and it was difficult to dissociate the ExoX bound to MutL.

MutL stimulates the exonuclease activity of ExoX

The effect of MutL on the exonuclease activity of ExoX towards dsDNA was tested using a 2022 bp dsDNA as substrate. Excision was very weak when the 2022 bp dsDNA substrate was added to the reaction mixture in a 1:4 ratio (dsDNA:ExoX). However, the excision reaction was rapid when MutL was added at a molar ratio of 1:1 (MutL:ExoX) or more (Fig. 3a). Stimulation of the exonuclease activity of ExoX depends on MutL concentration: at the highest MutL concentration tested (168 nM), all the DNA was digested within the 10-min incubation time (Fig. 3a). MutL and all the MutL mutants used were free of contaminating nucleases (SI Fig. 2).

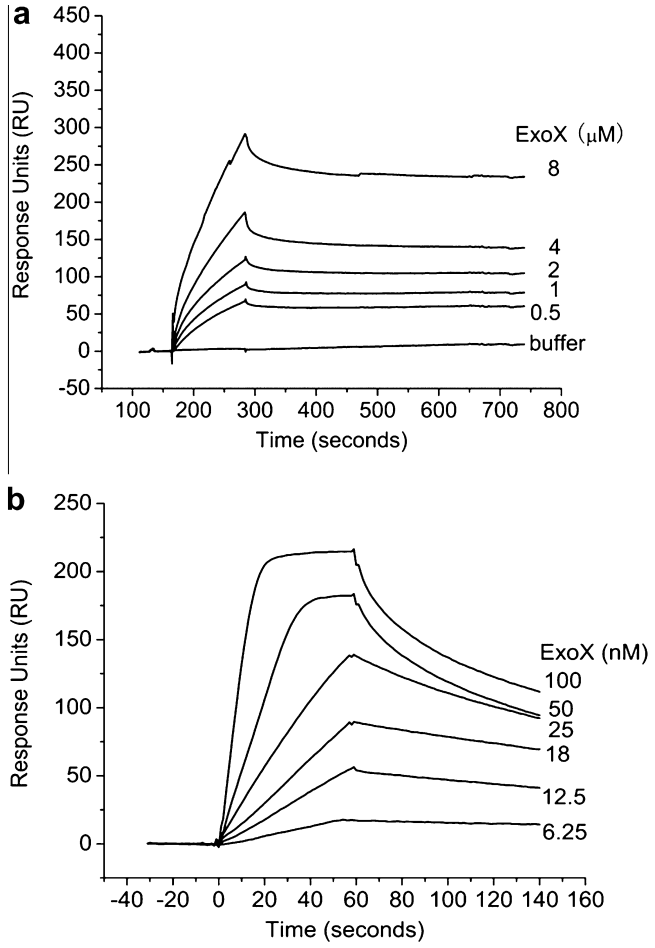

Fig. 2. ExoX interacts with MutL and dsDNA. For kinetic measurements, 749 RU MutL-SBP (a) and 140 RU dsDNA (b) were immobilized onto a sensor chip as described in the Materials and Methods. The indicated concentrations of ExoX were passed over the chip.

Table 1
Kinetic constants of interactions between ExoX and dsDNA and MutL.

Interaction	K_a (M^{-1} S^{-1})	K_d (S^{-1})	K_A (M^{-1})	K_D (M)
ExoX and dsDNA	7.08×10^5	6.3×10^{-3}	1.12×10^8	8.9×10^{-9}
ExoX and MutL	1.13×10^3	2.09×10^{-4}	5.41×10^6	1.85×10^{-7}

Stimulation of ExoX by MutL is ATP-independent

MutL is an ATPase [28–30] and its ATP binding and/or hydrolytic activity is essential in many processes. This prompted us to ask whether ATP regulates the stimulation of ExoX by MutL. We therefore compared the stimulation of ExoX by MutL in the presence and absence of ATP. Interestingly, we found that ATP has a little negative effect on the stimulation of ExoX by MutL (Fig. 3b).

Stimulation of ExoX does not require the DNA-binding activity of MutL

We used MutL-R266E, defective for DNA binding [29,31,32], to test whether the DNA-binding activity of MutL has an effect on the stimulation of ExoX. Interestingly, we found that MutL-R266E was more efficient than wild-type MutL in promoting the excision activity of ExoX (Fig. 3c). The interaction between ExoX and MutL-R266E was tested and we found that the R266E mutation enhanced the interaction nearly twofold (Fig. 4a). This result made us suspect that ionic interactions play a major role in the MutL–ExoX interaction. We therefore tested the MutL–ExoX interaction in different

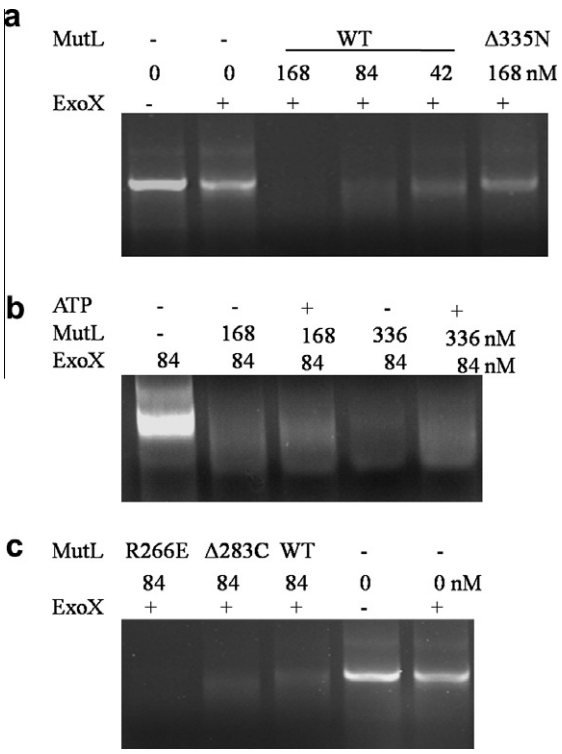

Fig. 3. Stimulation of the ExoX exonuclease activity by MutL or MutL mutants. For (a) and (c), reaction mixtures contained 10.5 nM dsDNA substrate, 42 nM ExoX, and indicated concentrations of MutL or MutL mutants. The reaction mixture was incubated at 37 °C for 10 min. (a) MutL was added in increasing concentrations (42, 84, 168 nM) and MutLΔ335N was added at a final concentration of 168 nM. (b) The reaction mixtures contained 21 nM dsDNA substrate, 84 nM ExoX and indicated concentrations of MutL in the presence or absence of 2 mM ATP. (c) The experiment was performed as in (a), except that MutL, MutLΔ283C and MutL-R266E were added at a final concentration of 84 nM.

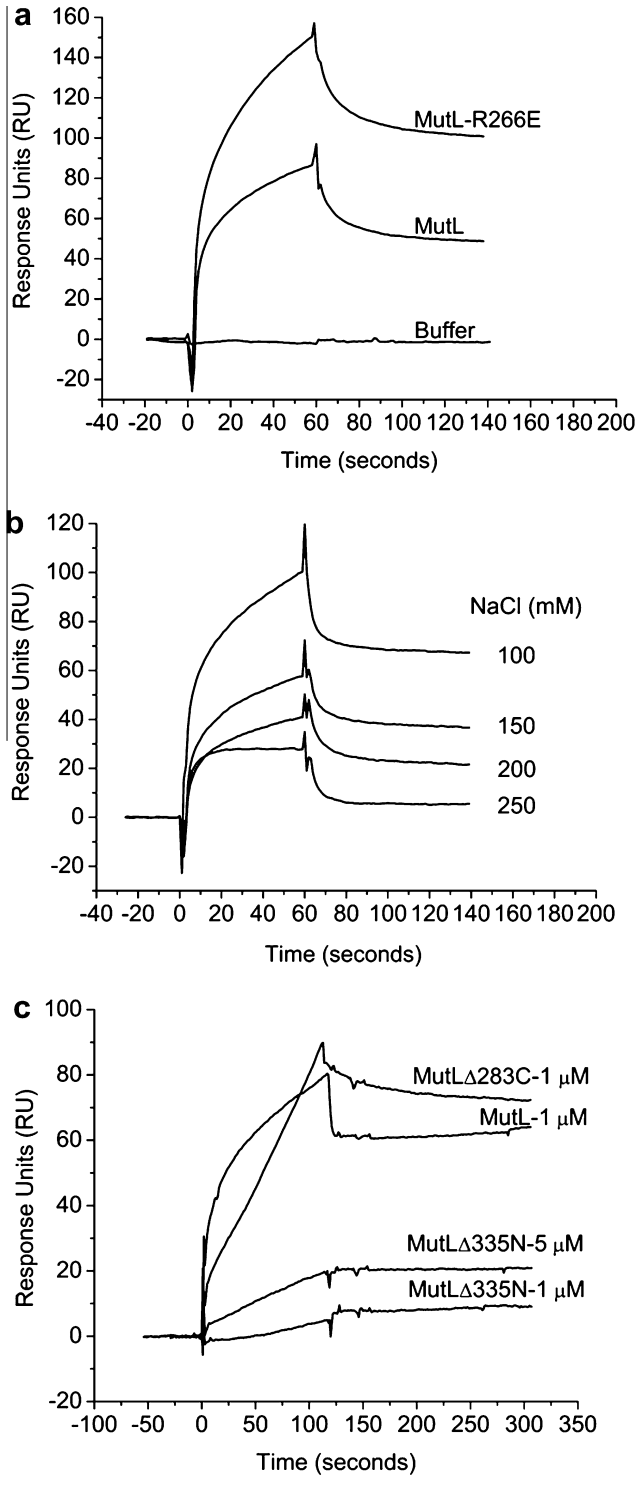

Fig. 4. MutL and MutL mutants interact with ExoX as measured by SPR. For (a) and (b), 2500 RU ExoX–SBP protein was immobilized on a SA chip and the concentration of protein passed over the chip was 2 μM. (a) MutL or MutL-R266E were passed over the chip in running buffer containing 125 mM NaCl. (b) MutL were flowed over the chip in running buffer contained the indicated NaCl concentrations. For (c), 2000 RU ExoX–SBP protein was immobilized on a SA chip and indicated concentrations of MutL or MutL truncation mutants (MutLΔ283C and MutLΔ335N) were passed over the chip in running buffer containing 125 mM NaCl.

NaCl concentrations. The association between ExoX and MutL was strongest at 100 mM NaCl and appeared progressively weaker at higher salt concentrations (Fig. 4b), suggesting that ionic interactions contributed to the ExoX and MutL interaction.

The 335 N-terminal amino acids of MutL are essential for functional interactions

The secondary structures of the *E. coli* MutL are located in the N-terminus and the C-terminus, while the intermediate section (336–438 aa) is predicted to form random coils [33,34]. N-terminal and C-terminal deletions of MutL were generated by gene manipulation in order to identify the location of the functional interaction domain. We tested the effect of these two deletion mutants on the excision activity of ExoX. As shown in Fig. 3a and c, compared with wild-type MutL, MutLΔ335N was inefficient and MutLΔ283C was as efficient as wild-type MutL in promoting the excision activity of ExoX. We then tested the interaction between ExoX and these two deletion MutL mutants. At a concentration of 1 μM, the interaction between the N-terminal deletion mutant MutLΔ335N and ExoX was very weak compared with wild-type MutL, whereas the interaction between the C-terminal deletion mutant MutLΔ283C and ExoX was a little stronger than that of wild-type MutL. The response level of MutLΔ335N was slightly elevated when the concentration was increased to 5 μM, but was still much lower than that of 1 μM MutL (Fig. 4c). These data suggest that the 335 N-terminal amino acids of MutL are essential for both the interaction with ExoX and the stimulation of ExoX activity.

Discussion

ExoX is a distributive exonuclease and thus is less efficient than other progressive exonucleases. A cofactor may be required to elevate its efficiency. Here we show that the interaction between MutL and ExoX makes ExoX more efficient in the excision of dsDNA and this stimulation is independent of ATP (Fig. 3a and b).

Since MutL was free of exonuclease activity (SI Fig. 2), we reasoned that its promotion of ExoX activity could be by one of two regulation mechanisms, either via MutL–ExoX interactions, or MutL–DNA interactions. The latter possibility was excluded using a MutL point mutant (MutL-R266E) which had significantly reduced DNA-binding affinity and could promote the excision even more efficiently than wild-type MutL (Fig. 3c). Thus, it seems most likely that it is the interaction between MutL and ExoX that makes ExoX more efficient in the excision of dsDNA.

To analyze the functional interaction between MutL and ExoX, we constructed two deletion mutants of MutL. The results suggest that the N-terminus of MutL mainly contributes to the functional interaction with ExoX through ionic interactions. Since the C-terminal region of MutL is essential for its dimerization [34] and our data have shown that it is not necessary for the interaction or promotion of ExoX, we believe that the MutL monomer can interact with ExoX and promote its ExoX activity.

A working model for MutL promotion of ExoX excision is proposed in Fig. 5. ExoX is a 3′–5′ exonuclease, which can digest dsDNA from both ends. For clarity, in the proposed model we only show the excision from one end. For the following reason, we propose that ExoX first binds to the dsDNA ends. Our SPR data have shown that ExoX bound to dsDNA (Fig. 2b and Table 1) with a K_D of 8.9 nM, which is many times higher than that for MutL bound to dsDNA (K_D > 5000 μM) [29]. Without MutL (Fig. 5a), ExoX must dissociate and rebind to its DNA substrate during cycles of degradation and is thus not an efficient exonuclease. When MutL is added, ExoX recruits MutL to the DNA to form a stable complex and the reaction can then proceed by one of two mechanisms: (i) MutL and ExoX form a complex with a higher affinity for DNA and this complex then excises DNA in a highly progressive manner (Fig. 5b); (ii) the interaction of MutL with ExoX stimulates ExoX conformational change and the changed conformation of ExoX

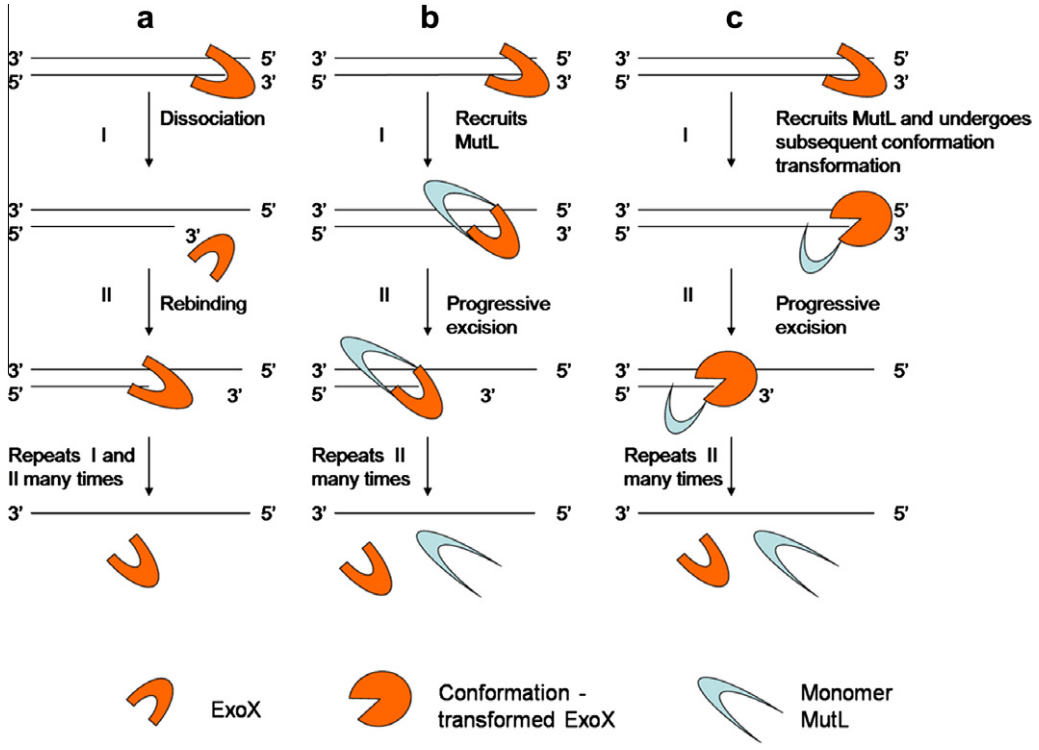

Fig. 5. Model for the mechanism of ExoX excision of dsDNA with the addition of MutL. Excision by ExoX (a) or ExoX + MutL (b) and (c) is shown. The model is described in the Discussion section.

has a higher affinity for DNA, making ExoX digest DNA in a highly progressive manner (Fig. 5c). Since MutL and ExoX formed a stable complex, other proteins might be involved in regulation MutL–ExoX complex *in vivo* so that it could stop excising when necessary.

ExoX functions as a redundant exonuclease in DNA recombination and repair and thus the cellular significance of the interaction between MutL and ExoX *in vivo* is difficult to test. The simplest explanation is that MutL may act in these processes to make ExoX more efficient. It would be of interest to test if MutL can elevate the excision efficiency of ExoX on ssDNA, and to determine whether MutL or its eukaryotic homologues affect the exonuclease activity of other DnaQ family members, especially whether MutLα can regulate the 3′–5′ exonuclease activity of the WRN protein in humans.

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.2010.07.011.

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