The β-Hairpin Motif of UvrB Is Essential for DNA Binding, Damage Processing, and UvrC-mediated Incisions*

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Received for publication, September 13, 2001, and in revised form, October 24, 2001
Published, JBC Papers in Press, October 30, 2001, DOI 10.1074/jbc.M108847200

UvrB plays a major role in recognition and processing of DNA lesions during nucleotide excision repair. The crystal structure of UvrB revealed a similar fold as found in monomeric DNA helicases. Homology modeling suggested that the β-hairpin motif of UvrB might be involved in DNA binding (Theis, K., Chen, P. J., Skorvaga, M., Van Houten, B., and Kisker, C. (1999) EMBO J. 18, 6899–6907). To determine a role of the β-hairpin of *Bacillus caldotenax* UvrB, we have constructed a deletion mutant, Δβh UvrB, which lacks residues Gln-97–Asp-112 of the β-hairpin. Δβh UvrB does not form a stable UvrB-DNA pre-incision complex and is inactive in UvrABC-mediated incision. However, Δβh UvrB is able to bind to UvrA and form a complex with UvrA and damaged DNA, competing with wild type UvrB. In addition, Δβh UvrB shows wild type-like ATPase activity in complex with UvrA that is stimulated by damaged DNA. In contrast to wild type UvrB, the ATPase activity of mutant UvrB does not lead to a destabilization of the damaged duplex. These results indicate that the conserved β-hairpin motif is a major factor in DNA binding.

Nucleotide excision repair (NER) is a highly conserved DNA repair pathway found in bacteria, yeast, and man (1, 2). NER is remarkable because of the wide variety of chemically and structurally distinct DNA lesions that are substrates for this process (3). NER has been fully reconstituted from bacterial and mammalian proteins and can be viewed as four basic steps, damage recognition and processing, incision, repair synthesis, and ligation. One of the best-characterized NER systems is the UvrABC nuclease from *Escherichia coli* (4, 5). Repair by UvrABC is initiated when the trimeric complex of UvrA2B recognizes the damaged site. It has been suggested that the UvrA2B complex may locate damage through a limited helicase activity (6–8). However, more recent studies suggest that the strand-separating activity of the UvrA2B complex is not through a helicase-driven translocation step but in fact is due to local, relatively slow changes within the protein-DNA complex leading to a stable UvrB-DNA pre-incision complex and dissociation of the UvrA dimer (9–12). Once the UvrB-DNA complex has formed, UvrC, in what appears to be two different binding modes, first makes an incision four to five nucleotides 3’ to the modified nucleotide in an ATP-dependent step, which is followed by rapid incision seven nucleotides 5’ to the lesion in a step that does not require ATP hydrolysis (13). Recent work from Goosen and co-workers (14–17) strongly suggests, that in contrast to earlier reports (18, 19), UvrB has no intrinsic nuclease activity; 3’ incision is mediated by the N-terminal domain of UvrC and 5’ incision appears to be mediated by a nuclease center in the C-terminal domain of UvrC. After the incision reaction UvrD (helicase II) and DNA polymerase I are necessary and sufficient to release the excised oligonucleotide and allow UvrB and UvrC to participate in another round of incision (20, 21).

UvrB plays a central role in bacterial NER, participating in damage recognition, processing the DNA into a stable pre-incision complex, helping direct the activity of UvrC to perform the dual incisions, and finally staying bound to the non-damaged strand until being dislodged by DNA polymerase I (19, 22). UvrB contains six highly conserved sequence motifs, containing 10–40 amino acid residues each, that are found in all DNA helicases (23, 24). Three laboratories have independently solved the crystal structures of UvrB from thermophilic bacteria (25–28). UvrB is folded into five structural domains, 1a, 1b, 2, 3, and 4. The structure of domain 4, disordered in crystals of the full-length protein, has been determined separately (29). Domains 1a and 3 contain the six helicase motifs, placing UvrB as a member of the helicase superfamily II (30).

Superpositioning of UvrB onto other helicase structures has revealed that UvrB domains 1a and 3 are structurally closely related to the monomeric helicase fold found in PcrA, NS3, and Rep (28). Domains 1b and 2 are unique to UvrB, the latter being a binding site for UvrA. Comparing the structure of UvrB with these helicase structures revealed that UvrB contains all the structural properties of a helicase that couple ATP binding and hydrolysis to domain motions. However, if UvrB binds DNA in a similar manner as observed in the DNA complexes of these helicas, then the translocated DNA strand would be partially covered by a flexible β-hairpin structure. This unique structural element (see Figs. 1, A and B) connecting domains 1a and 1b was found to be highly conserved in all bacterial species. The β-hairpin is held in place with respect to domain 1b by two salt bridges and hydrophobic interactions at the base and the tip of the hairpin. Similar β-hairpin motifs found in PcrA and RNA polymerase II are thought to be essential for the strand opening performed by these two proteins (31, 32). We have previously shown that the DNA in the UvrB-DNA complex is...
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The gel was dried and exposed against Storage Phosphor Screen (Molecular Dynamics) overnight at room temperature.

UvrABC Incision Assay—The 5′ terminaly labeled F

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P-50 dsDNA substrate (2 nm) was incised by UvrABC (20 nM UvrA, 60 nM UvrB, 50 nM UvrC) in 20 μl of UvrABC buffer (50 mm Tris/Cl (pH 7.5), 150 mm NaCl, 1 mm MgCl2, 1 mm EDTA, 5 mm ATP, 2 mm dithiothreitol) and was incubated at 42 °C for 1 h. The reaction was quenched with 5 μl of stop solution (25% (v/v) Ficoll, 1% SDS, 0.1 mm EDTA, 0.25% orange G) and heated for 2 min at 85 °C, and the entire sample was then loaded onto a 15% denaturing polyacrylamide gel equilibrated with Tris-borate EDTA running buffer. Electrophoresis was carried out at 400–600 V for 1–2 h. The gels were processed as described above.

CD Spectroscopy—CD spectra were measured at 20 °C on an Aviv model 62 ADS spectrometer using rectangular cells with a path length of 0.2 mm. Proteins were measured at concentrations between 0.6 and 1.4 mg/ml in a buffer containing 500 mm KF and 10 mm K2HPO4 at pH 7.4. UV absorption at 280 nm was used to determine protein concentrations. Absorbance measurements were used to determine the extinction coefficients of wild type UvrB (658 amino acids) and UvrBΔβ (643 amino acids) were calculated from the primary sequence to 33,280 and 30,720 liters/mol/cm, respectively. The CD spectra were sampled at 1-nm intervals with a time constant of 1 s and 10 scans for both samples and blanks, resulting in an acquisition time of 1 h for each spectrum.

Oligonucleotide-releasing Assay—The reaction mixture contained 50 nm UvrA, 100 nm UvrB, and ~8 fmol (in dsDNA circles) of helicase substrate (HS1F-M13mp19) in buffer A1 (50 mm Tris/Cl (pH 7.5), 150 mm NaCl, 10 mm MgCl2, 2 mm ATP, 5 mm dithiothreitol) and was incubated at 37 °C for various time intervals. The reaction was stopped with 5 μl of stop solution (5% (v/v) glycerol, 1% SDS, 0.1 mm EDTA, 0.25% orange G), and the entire sample was loaded on 12% non-denaturing polyacrylamide gel in Tris-borate EDTA running buffer. Electrophoresis was run at 120–150 V for 1–2 h, and the gels were processed as described above.

ATP Hydrolysis Assay—The conversion of ATP to ADP by the UvrABC system was determined by a coupled enzyme assay system consisting of pyruvate kinase and lactate dehydrogenase to link the hydrolysis of ATP to the oxidation of NADH. The assay mixture consisted of 50 mm Tris/Cl (pH 7.5), 50 mm NaCl, 4 mm MgCl2, 1 mm dithiothreitol, 20 units/ml lactate dehydrogenase, 20 units/ml pyruvate kinase, 2 mm phosphoenol pyruvate, 0.15 mm NADH and 200 μM Uvr proteins in the presence or absence of 50 ng of UV-irradiated DNA substrate. DNA substrate was prepared by exposure of pUC18 DNA to 200 J/m2. B. caldotenax UvrA, UvrB, and UvrC proteins were preheated to 55 °C for 10 min to inactivate E. coli contaminant protein activities. The reaction mixture (0.5 ml) was allowed to equilibrate at 37 °C, and the assay was initiated by the addition of ATP (0.5 mm). The rate of ATP hydrolysis was calculated from the linear change in absorbance at λ = 340 nm over 30 min, which accompanied the oxidation of NADH, using a Beckman spectrophotometer. Determinations were performed in duplicate and done three separate times. Data are reported as the means ± S.D.

RESULTS

To test our podack DNA binding model and the importance of the β-hairpin motif in the recognition of DNA damage, we have constructed a β-hairpin deletion mutant of the B. caldotenax UvrB protein, designed as Δβ UvrB, with amino acid residues from Gln97 to Asp112 removed and the resulting gap bridged by a glycine residue (Fig. 1, A and B). In the resulting deletion mut in the upper half of the β-hairpin was disabled. To test the properties of this mutant, we reconstituted the B. caldotenax UvrABC nucleosome system with purified UvrA, UvrB, and UvrC (Fig. 1C), each obtained via intein fusion proteins.

UvrABC-mediated Incision of a Fluorescein-containing 50-bp Duplex Using the UvrB β-Hairpin Deletion Mutant—We first investigated the effect of ΔβUvrB on UvrABC endonuclease
mediated-incision. The substrate was a 50-bp duplex containing a fluorescein moiety in the middle of the top strand (position F_26, see Fig. 2A), labeled at its 5' terminus with [γ-32P]ATP. Results of the UvrABC endonuclease incision kinetics of F_26-50 dsDNA are shown in Fig. 3. Panel A contains data for wild type UvrB, panel B contains data for Δβh UvrB, and panel C summarizes the incision kinetics. The results show that Δβh UvrB does not support UvrABC-mediated incision of substrate DNA. The residual incision of ≤5–6% represents the level of background for the substrate used. Clearly, deleting the β-hairpin of UvrB disrupts one of the steps that lead to incision of the damaged DNA.

Loading of the Δβh UvrB Protein onto the Site of Damage—The failure of Δβh UvrB to confer endonuclease activity to the UvrABC system might be due to failure to recognize the damage or failure to incise the damage after successful recognition. We used a gel mobility shift assay to test whether the intermediate between these processes, the UvrB-DNA pre-incision complex, is formed with the Δβh UvrB mutant (Figs. 4 and 5). The Δβh UvrB protein does not form a stable complex with the damaged DNA neither at low concentrations (1–20 nM; Fig. 4A) nor at higher amounts (50–200 nM; Fig. 4B), whereas loading of wild type UvrB is very efficient, even at 5 nM (Fig. 4A, lane 7). It is interesting to note that the band corresponding to the UvrA2-DNA complex (Fig. 4B, lane 2) migrates slightly faster than the samples containing the Δβh UvrB protein (Fig. 4B, lanes 4–6). This slower mobility band probably represents the UvrA2Δβh UvrB-DNA complex. Further investigation was necessary to establish whether Δβh UvrB is able to bind to UvrA, we have conducted competition experiments between the mutant and the wild type UvrB for binding to UvrA and F_26-50 dsDNA. In these experiments (Fig. 5) there is a clear difference in mobility between the UvrA2-DNA and UvrA2Δβh UvrB-DNA complexes (Fig. 5, compare lane 2 with lanes 3–5). Increasing amounts of Δβh UvrB (10, 50, 100 nM) at a constant wild type UvrB concentration (5 nM) resulted in a significant reduction of the amount of wt UvrB-DNA complex (Fig. 5, lanes 4–6 versus lane 8). This dominant negative effect of Δβh UvrB supports the idea that Δβh UvrB is properly folded and shows that it is capable of interacting with UvrA, resulting in the reduction of the amount of UvrA molecules available to interact with wild type UvrB.

CD Spectra of Wild Type and the β-Hairpin Deletion Mutant UvrB—Fig. 6 shows CD spectra of wild type (filled ovals) and Δβh (open ovals) UvrB proteins, respectively. The results exhibit nearly identical CD spectra for both wild type and mutant proteins, indicating that the deletion of the β-hairpin motif in UvrB does not affect the global folding of the protein.

Strand Destabilizing Activity of Δβh UvrB—In our padlock DNA binding model, we proposed that the β-hairpin of UvrB requires at least 5 base pairs of DNA to be disrupted so that the β-hairpin could be inserted between the strands of DNA. The limited strand opening by the UvrA2B complex has been shown previously to be important for dynamic recognition of DNA damage (11, 12) and has been called a limited helicase activity (6, 7). To evaluate the importance of the β-hairpin motif for the presumed helicase activity of the UvrA2B complex, we assayed Δβh UvrB in a strand destabilization assay that measures the release of a radioactively labeled 26-mer containing fluorescein annealed to a single-stranded DNA circle (M13mp19+) strand. The results are shown in Fig. 7, with kinetics of the 26-mer release summarized in panel C. Although wild type UvrB supports the release of the fluorescein-containing 26-mer very efficiently, reaching about 50% release of oligomer after 60 min, the β-hairpin deletion mutant has very low, if any, activity. It is critical to realize that the “release” of the oligomer is assayed after the addition of a stop buffer containing 1% SDS and 0.1 mM EDTA.

Incision of Strand-destabilizing Substrate by Δβh UvrB—If UvrB is capable of true strand displacement like a bona fide helicase, then the displaced strand would be single-stranded. However, single-stranded damaged DNA is not a substrate for the UvrABC system. As can be clearly seen in Fig. 7D, the helix-destabilizing substrate, a 5’-labeled 26-mer containing a fluorescein adduct annealed to M13mp19 ssDNA, was incised by the UvrABC nuclease system. The incision efficiency supported by wild type UvrB was ~55% (at 42 °C for 1 h; Fig. 7, panel D, lane 2), whereas the Δβh UvrB mutant did not support any incision of the 26-mer-fluorescein/M13 substrate. Based on this incision of the strand-displacement substrate with wild type UvrB (as part of the UvrABC endonuclease), we suggest that UvrA2B does not completely release the damage-containing 26-mer from a ssDNA circle until SDS is added as part of the stop buffer. Therefore, we feel it is inappropriate to call this activity a true helicase, and we suggest it is better to call this property of UvrA2UvrB a strand-destabilizing activity.
that ATP binding/hydrolysis is absolutely required for NER (6). In our padlock model (25) we suggest that the formation of a stable UvrB-DNA pre-incision complex requires free energy, which might be available either through ATP hydrolysis by UvrA2B or as a result of complex formation. To test whether the altered DNA binding properties of Δβh UvrB are due to an

![Diagram of DNA substrates used in this study. Panel A, Fβw-50 dsDNA substrate, 50-base pair duplex with fluorescein attached at position 26. Panel B, schematic representation of the helicase substrate, HS1F-M13mp19(+). The figure shows the complete nucleotide sequence of a fluorescein-containing 26-mer (bottom strand), HS1F, that has been annealed to single-stranded M13mp19(+) DNA (top strand). The position of the fluorescein adduct in the bottom strand is designated as a bold F.](http://www.jbc.org/)

![Figure 3. Δβh UvrB does not support incision of a fluorescein containing a 50-bp duplex. The Fβw-50 dsDNA substrate (2 nM) (sequence shown in Fig. 2A with a 5’ terminally labeled modified strand) was incubated with UvrA (20 nM), UvrB (60 nM), and UvrC (50 nM) at 55 °C for 1 h. The samples were analyzed by PAGE under denaturing conditions. Panel A, wt UvrB; Panel B, Δβh UvrB. Panel C, kinetics of the incision reaction.](http://www.jbc.org/)
altered ATPase activity, we have examined this activity for both wild type UvrB and Δβh UvrB (Table I). By itself, Δβh UvrB has a very low ATPase activity at 37°C (2.88 μmol of ATPase/min/mg of protein), similar to wild type UvrB (1.40 μmol/min/mg). In this respect, B. caldotenax UvrB resembles E. coli UvrB that has a cryptic ATPase activity. It has been shown that full ATPase activity of UvrB requires the presence of both UvrA and DNA (33). Our data show that the ATPase activity of Δβh UvrB is not affected by deletion of the β-hairpin motif. In fact, in the presence of UV-irradiated DNA, the ATPase activity of the UvrAΔβhUvrB complex is higher than that of the UvrA wt UvrB complex (29, 22 μmol/min/mg, respectively). This is further evidence that UvrA and Δβh UvrB interact, as was suggested from our previous experiments (gel mobility shifts, CD spectra, helicase assay). The deletion of the β-hairpin does not interfere with the ATP hydrolysis by UvrB in the UvrAΔB complex, but apparently the free energy of hydrolysis is not coupled to proper processing of the DNA that is necessary for UvrC binding and incision.

**DISCUSSION**

Mutational analysis of UvrB has not yet identified which parts of UvrB are involved in DNA binding (reviewed in Ref. 28). One complication is that UvrB has an ATPase activity that is stimulated by DNA binding and is necessary for the formation of the pre-incision complex. Thus, defects of UvrB mutants defective in DNA binding might be due to defects in ATP binding/hydrolysis and vice versa. So far, mutants characterized for both properties showed either inactivation of both or no effect on either. Most of the mutations that affect DNA binding are located in the six highly conserved sequence motifs found in helicases of superfamily I and II. In a previous report (25) we proposed a three-dimensional structure of the UvrB protein from the thermophilic bacterium B. caldotenax. The crystal structure of B. caldotenax UvrB has a significant level of similarity with that of helicase NS3 (34). By superposition of B. caldotenax UvrB with the helicase domains of NS3 complexed with DNA, we have hypothesized a model for the UvrB-DNA pre-incision complex, which has a pivotal role in the mechanism of damage recognition by the UvrABC system. In our model we propose a padlock-like binding mode of UvrB to wrap around one DNA strand by inserting a β-hairpin between the two strands of DNA (28).

To test our model and investigate the functional role of the β-hairpin motif, we constructed a β-hairpin deletion mutant (Δβh UvrB) in which residues 97–112 are replaced by a glycine, removing the tip of the β-hairpin. Data presented here show that the (β-hairpin deletion mutant 1) is greatly reduced in its ability to support incision, 2) is unable to bind to a damage-containing duplex, 3) cannot destabilize a damage-containing 26-mer, and 4) has retained the ability to hydrolyze ATP in a UvrA and damaged DNA-dependent manner. Thus, functions of UvrB required for the formation of the UvrB-DNA complex, namely UvrA binding and ATP hydrolysis, are not disrupted in the deletion mutant. Nevertheless, Δβh UvrB is unable to form a stable complex with DNA, strongly suggesting that the deleted residues are directly involved in DNA binding.
experiments have described the activity of UvrA2B as helicase-UvrC binding. It is important to note that although these binding/hydrolysis to allow UvrB to facilitate cleavage upon torqued, and it is believed that it is this step that requires ATP UvrB-DNA complex. The DNA in this complex is greatly dis-

The figure shows the kinetics of 26-mer release by wt UvrB (panel A), Δβh UvrB (panel B), and graphic comparison of both wt and Δβh UvrB (panel C). Panel D, in-
cision of a 26-mer containing fluorescein, HS1F-M13mp19(−) DNA (8 fmol) with a 5′ terminally labeled modified strand was incubated with UvrA (20 nM), UvrB (60 nM), and UvrC (50 nM) at 55 °C for 1 h. The samples were analyzed by PAGE under denaturing conditions.

### Table I

| Samples                        | ATPase activity (μmol of ATP hydrolyzed/μmol of protein/min) |
|--------------------------------|-------------------------------------------------------------|
| UvrA                           | 13.2 ± 0.6                                                  |
| UvrA + UV fluorescein DNA      | 17.0 ± 1.0                                                  |
| UvrB                           | 1.4 ± 0.1                                                   |
| UvrB + UV fluorescein DNA      | 1.4 ± 0.1                                                   |
| UvrA + UvrB                    | 18.3 ± 0.1                                                  |
| UvrA + UvrB + UV fluorescein DNA | 22.0 ± 0.5                                      |
| Δβh UvrB                       | 2.8 ± 0.1                                                   |
| UvrA + Δβh UvrB                 | 19.0 ± 0.6                                                  |
| UvrA + Δβh UvrB + UV fluorescein DNA | 29.0 ± 1.0                                      |

During the late 1980s and early 1990s Grossman and co-

Because of these discrepancies Gordienko and Rupp (11) developed a “helicase scanning model” of damage recognition (6–8). In this model, UvrA₂B can displace short oligo-

We hypothesize that there are five critical regions in UvrB that are necessary and sufficient for DNA damage binding and processing: 1) a damage recognition pocket located at the base of the β-hairpin; 2) a flexible β-hairpin, which acts as a padlock to secure the non-damaged strand in place; 3) an ATP binding site, which facilitates conformational changes in UvrB; 4) the coiled-coiled C terminus of UvrB, which interacts with UvrC; and finally, 5) residues in domain 3 that contain helix motifs IV-VI which help drive a conformational change in the DNA, leading to incision. How might the β-hairpin motif participate in allowing UvrB to bind and process damage? In our padlock DNA binding model of UvrB, the β-hairpin must first open to accept a strand of DNA and then close to lock one DNA strand; we favor the non-damaged strand, forming a stable UvrB-DNA interaction. Taking a closer look at the anatomy of the β-hairpin reveals four critical regions, three of which were removed in the Δβh mutant. The tip of the β-hairpin is hydrophobic in character and interacts with hydrophobic residues in domain Ib. Two salt bridges located in the middle of the hairpin provide further strength to the lock. Preserved in the Δβh mutant is an aromatic base containing several Tyr and Phe residues that are 100% conserved in all bacterial species examined to date. We propose that these residues are part of the damage recognition pocket. However, the interaction energy of these residues with the damaged strand without the strong padlock holding onto the non-damaged strand are apparently insufficient to provide sufficient binding energy in the Δβh mutant for productive
binding (Fig. 4) and incision (Fig. 3). In this regard it is interesting to note that UvrB binds to single-stranded oligonucleotides with a $K_d$ of 0.83–1.5 $\mu M$ and has an increased affinity for damaged DNA (19, 36). Because all our experiments were performed with UvrB and DNA concentrations well below this $K_d$, it is not unexpected that we did not see any productive binding or incision.

Having formed a stable UvrB-DNA complex, how is incision achieved? It is believed that UvrC is recruited to the UvrB-DNA complex through a coiled-coiled domain at the C terminus of UvrB. We envision that UvrB uses the closure of domain III through ATP binding and/or hydrolysis to further distort the damaged DNA strand in order to drive the phosphate backbone into the nucleosome cleft at the N terminus of the UvrC to initiate the 3’-incision (37). However, the ATPase activity of Δθh UvrB mutant is still active and actually more robust than wild type (Table I), suggesting that futile cycles of ATP hydrolysis occur within the lesion.

In summary, our data clearly indicate that the upper part of the β-hairpin (residues 97–122) is absolutely required for DNA damage recognition by the UvABC system, since the Δθh UvrB failed to bind the damaged DNA, support incision, and had no strand destabilizing activity. These results are simply not due to a large conformational change in Δθh UvrB, since CD experiments indicate that the deletion mutant and wt protein have nearly identical spectra. This is further supported by the ability of the mutant protein to interact with UvrA and demonstrate an ATPase activity that is induced in the presence of UvrA and UV-irradiated DNA (Table I). We are currently studying the importance of the individual amino acid residues within the β-hairpin as well as those residues presumably involved in the formation of salt bridges that might be essential for the proper function of the β-hairpin.

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