Identification of a Substrate Recognition Domain in the Replication Stress Response Protein Zinc Finger Ran-binding Domain-containing Protein 3 (ZRANB3)*

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Genomic replication is a highly challenging task. The DNA replication machinery must precisely duplicate billions of base pairs while tolerating a multitude of obstacles including damaged DNA, collisions with transcriptional machineries, unusual DNA structures, and other difficult to replicate sequences (1). Many of these obstacles stall replication forks and activate replication stress responses that stabilize and restart persistently stalled forks. These mechanisms include fork remodeling to regress replication forks into a chicken foot DNA structure (2, 3). Fork regression may facilitate DNA repair or template switching to bypass the obstruction (3).

Several members of the SNF2 family of DNA-dependent ATPases including SMARCAL1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1),3 HLTF (helicase-like transcription factor) and ZRANB3 (zinc finger Ran-binding domain containing 3) are replication stress response proteins that catalyze fork remodeling including fork regression (4–6). The replication stress response is essential to complete replication accurately. Therefore, defects in this response cause human disease (1). For example, bi-allelic loss of function mutations in SMARCAL1 cause Schimke-Immunooosseous Dysplasia (SIOD) (7). SIOD is a developmental disorder characterized by growth defects, immune-deficiency, and renal failure. Recent studies also suggest that SIOD may be a cancer predisposition syndrome (8–10). HLTF is silenced in colorectal cancer and ZRANB3 is mutated in endometrial cancers suggesting that both may be tumor suppressors (11, 12).

SMARCAL1 localizes to stalled replication forks through an interaction with RPA (13–16). The RPA interaction also regulates SMARCAL1 enzymatic activity to ensure that it regresses only stalled forks (17, 18). Although HLTF is present at replication forks, it is unclear if it is recruited through a protein-protein interaction or simply by its structure-specific DNA binding activity (19). ZRANB3 is recruited by binding to poly-ubiquitinated PCNA (5).

The enzymatic activities of SMARCAL1 and HLTF are dependent on a SNF2 ATPase motor domain and a substrate recognition domain (SRD) that is thought to mediate binding to specific structures at stalled replication forks. The SRD of SMARCAL1 is its HARP2 domain, which is required for SMARCAL1 binding to branched DNA structures as well as DNA-dependent ATPase and fork regression activities (4, 20). The HARP domain is structurally related to the damage recognition domain of the XPB helicase and the mismatch recognition domain of MutS (20). The SRD in HLTF is its HIRAN domain, which is unrelated in sequence and structure to the HARP domain and interacts with the exposed 3’ end of small DNA flaps (19–21). The HIRAN domain is also important for HLTF mediated fork regression activity (19, 22). In both SMARCAL1 and HLTF, mutations in the HARP or HIRAN domains interfere with their ability to bind DNA (4, 19–21).

Yuan et al. reported that ZRANB3 contains a domain similar in sequence to the HARP domains of SMARCAL1 (23). However, they reported that deletion of this putative SRD domain

mutants, L760A/D761A/I762A; MT2 mutants, W790A/S791A/S792A; PCNA, proliferating cell nuclear antigen; RPA, replication protein A; SIOD, Schimke-Immunooosseous Dysplasia; SRD, substrate recognition domain; ssDNA, single-stranded DNA; ZRANB3, zinc finger Ran-binding domain containing 3.

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3 The abbreviations used are: SMARCAL1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1; dsDNA, double-stranded DNA; HARP, HepA-related protein; HIRAN, HIP116 Rad5p N-terminal; HLTF, helicase-like transcription factor; MT1

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inactivates its strand annealing activity without interfering with DNA binding or DNA-dependent ATPase activity (23). Given the apparent differences in the reported activities of the SMARCAL1 HARP and ZRANB3 HARP-like domains, we revisited the requirements for ZRANB3 to bind DNA, hydrolyze ATP and catalyze fork remodeling. We define a ZRANB3 SRD that is essential for all three functions and define the ZRANB3 minimal enzymatic unit for fork remodeling as containing only the SNF2 ATPase domain and its SRD.

Experimental Procedures

Recombinant DNA Cloning—All ZRANB3 expression vectors and amino acid numberings are based on ZRANB3 isoform 2. The 1–501/720–869 minimal enzymatic unit contains a (GGGGG)5 linker (24). All vectors and oligonucleotide sequences used for PCR and mutagenesis are available upon request.

Recombinant Protein Expression and Purification—FLAG-ZRANB3 proteins (WT (wild type), Δ712–818, K163D (mutation in walker A motif in ATPase domain that impairs ATP hydrolysis), 1–501, 1–650, 1–869, ΔNZF, ΔDH, ΔAPIM, Δ651–720, Δ712–794, Δ795–859, L760A/D761A/I762A (MT1), W790A/S791A/S792A (MT2)) were purified from HEK293T cells as previously described (4) with the following modifications: cells were lysed for 40 min on ice in lysis buffer (20 mM Tris, pH 7.5, 150 mM NaCl, 1 mM DTT, 0.2 mM PMSF, 5 μg/ml aprotinin, 5 μg/ml leupeptin, 0.1% Triton X-100, 0.1 mM EDTA). Cleared cell lysate was incubated with FLAG-M2 beads (Sigma F2426, EZ View Red Anti-FLAG M2 Affinity gel) for 4 h at 4 °C. Beads were washed twice with lysis buffer, once with LiCl buffer (10 mM HEPES, pH 7.9, 0.3 mM LiCl, 20% glycerol, 0.2 mM EDTA, 0.1% Triton X-100, 1 mM DTT, 0.2 mM PMSF, 1.5 mM MgCl2, 5 μg/ml aprotinin, 5 μg/ml leupeptin, 0.1% Triton X-100, 0.1 mM EDTA), and twice with the elution buffer (20 mM HEPES, pH 7.9, 0.1 mM KCl, 1.5 mM MgCl2, 0.2 mM EDTA, 20% glycerol, 0.01% Nonidet P-40, 1 mM DTT, 0.2 mM PMSF, 5 μg/ml aprotinin, 5 μg/ml leupeptin). Proteins were eluted using 300 μg/ml FLAG peptide (F3290 Sigma). FLAG-ZRANB3 protein from insect cells was purified using the same procedure as FLAG-SMARCAL1 (25).

GST-720–869 and GST-720–869 L760A/D761A/I762A (MT1) were purified from ArcticExpress Escherichia coli (Agilent Technologies). Cells were grown at 37 °C and upon reaching an OD600 protein expression was induced with 1 mM IPTG and grown at 16 °C overnight. The cell pellet was solubilized in lysis buffer (25 mM Tris, pH 8.0, 50 mM NaCl, 0.1 mM EDTA, 5% glycerol, 1 mM DTT, 0.1 mM PMSF, 5 μg/ml aprotinin, 5 μg/ml leupeptin) and lysed by sonication. Triton X-100 was added to reach a final concentration of 1% and the lysate was incubated on ice for 30 min. Following high-speed centrifugation, the lysate was incubated with GST beads for 4 h at 4 °C. Afterward, the beads were washed three times with lysis buffer containing 1% Triton X-100. Protein was eluted with elution buffer (75 mM Tris, pH 8, 15 mM glutathione, 0.1 mg/ml leupeptin), and dialyzed overnight at 4 °C (dialysis buffer: 20 mM Tris, pH 8.0, 1 mM DTT, 0.1 mM EDTA, 20% glycerol, 5 μg/ml leupeptin, 5 μg/ml aprotinin, 0.2 mM PMSF). Dialyzed samples were applied to a heparin column and eluted with increasing concentration of KCl (50 mM, 75 mM, 150 mM, 300 mM). Fractions containing the desired protein were combined and concentrated using a Millipore 10,000 MWCO protein concentration filter.

Alignment—ZRANB3 protein sequence alignments were performed using Clustal Omega. The HARP1 and HARP2 sequences were obtained from the boundaries identified previously (4, 20). Secondary structure prediction was performed using POLYVIEW, PSIPRED, and JNETPRED prediction software (26–28).

DNA Substrate Assembly and Purification—The single-stranded (30nt), double-stranded (30nt), splayed arm, replication fork, fork regression, and fork restoration DNA substrates used for ATPase, DNA binding, and fork remodeling reactions were assembled and purified as described previously (4, 17, 18).

ATPase Assay—ATPase assays were conducted as previously described (25).

DNA Binding Assay—DNA binding was conducted largely as previously described (25). Briefly, protein was incubated with 10 nm of 32P-labeled DNA substrate at 30 °C for 30 min. Following incubation, 15% Ficoll was added to a final concentration of 2.5%. Samples were resolved on a 5% or 8% polyacrylamide gel in 1x TBE (100 mM Tris, 90 mM boric acid, 2 mM EDTA) at 40 V for 180 min at 4 °C.

Nuclease Assay—Nuclease assays were conducted as previously described (29). Briefly, protein was incubated with 10 nm of 32P-labeled splayed arm substrate for 30 min at 30 °C in nuclease buffer (50 mM Tris, pH 7.5, 50 mM NaCl, 5 mM MgCl2, 2 mM ATP, 0.1 mg/ml BSA). The products were resolved on a 10% polyacrylamide gel in 1x TBE at 80 V for 80 min at room temperature.

Fork Remodeling Assay—Fork regression and fork restoration reactions were conducted as previously described (17, 18). For the fork regression reaction, 3 nm of protein was incubated with 3 nm of labeled leading strand gap regression substrate for increasing amount of time at 37 °C. For the fork restoration reaction, increasing amount of protein was incubated with 3 nm of the lagging strand gap restoration substrate for 30 min at room temperature. The products were resolved on an 8% polyacrylamide gel in 1x TBE at 80 V for 80 min at room temperature.

Results

Region 720–869 Is Highly Conserved and Necessary for ZRANB3 ATPase Activity—ZRANB3 is a DNA-dependent ATPase in the same SNF2 family as SMARCAL1 and HLTF (30). SMARCAL1 and ZRANB3 are both annealing helicases that re-anneal complementary DNA strands (25, 31) and catalyze replication fork remodeling reactions (4, 5). The SMARCAL1 HARP2 domain is required for SMARCAL1 to bind DNA, hydrolyze ATP, anneal DNA, and remodel replication forks (4, 20).

A previous study concluded that a region encompassing amino acids 712–818 in ZRANB3 contains a HARP-like domain that is required for ZRANB3 annealing helicase activity (23). However, unlike the SMARCAL1 HARP domain, the HARP-like domain was reported to be dispensable for DNA binding and ATPase activity. Fork remodeling was not tested. Due to the striking functional differences between the HARP and HARP-like domains, we revisited whether the HARP-like
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domain of ZRANB3 really shares similar functional properties to the SMARCAL1 HARP domains. We purified wild type (WT) and Δ712–818 ZRANB3 (Fig. 1A) and tested their ability to bind a splayed arm DNA substrate and hydrolyze ATP. In contrast to the previously published findings, purified Δ712–818 ZRANB3, which lacks the HARP-like domain, failed to bind a splayed arm DNA substrate (Fig. 1B). It also lacked DNA-stimulated ATPase activity (Fig. 1C). In contrast, WT ZRANB3 displayed both DNA-binding and DNA-dependent ATPase activity.

It is unclear whether deleting amino acids 712–818 generates a protein that is properly folded. Since important amino acids in the SMARCAL1 HARP domain have already been identified (4, 20), we attempted to generate a sequence alignment between the SMARCAL1 HARP domains and the ZRANB3 HARP-like domain to identify critical amino acids for mutagenesis. However, we were unable to find sufficient sequence similarity to generate a useful alignment. Therefore, using evolutionarily conserved regions of ZRANB3 as a guide, we designed and tested various deletion, truncation, and point mutants to determine regions within the protein that are necessary for DNA-dependent ATPase activity (Fig. 2A). Deletion of the NZF and APIM motifs, which bind polyubiquitinated PCNA (5), did not impair ATPase activity (Fig. 2B). Deletion of the HNH nuclease domain caused a modest but reproducible decrease in activity (Fig. 2B). Deletion of amino acids 651–720 also yielded an active enzyme (Fig. 2C). In contrast, ZRANB3 Δ712–794 and ZRANB3 Δ795–859 were both inactive (Fig. 2D).

![Figure 1](image1.png)

**FIGURE 1. Δ712–818 ZRANB3 does not bind DNA and cannot hydrolyze ATP.** A, Coomassie-stained SDS-PAGE gel of purified wild-type (WT) and Δ712–818 ZRANB3. B, Δ712–818 ZRANB3 and WT ZRANB3 were incubated with a splayed arm DNA substrate. To assess DNA binding, samples were resolved on a polyacrylamide gel and visualized by autoradiography. A representative experiment is shown. C, Δ712–818 ZRANB3 and WT ZRANB3 were incubated with a splayed arm substrate, and ATPase activity was measured. A representative experiment (of at least two replicates) is shown for each mutant.

![Figure 2](image2.png)

**FIGURE 2. Amino acids 721–869 are necessary for ZRANB3 DNA-dependent ATPase activity.** A, schematic and summary of results for the various deletion, truncation, and point mutants. Purified [β]ΔNZF, ΔNH, ΔAPIM motif deletion mutants; C, Δ651–720 deletion mutant; D, Δ712–794 and Δ795–859 deletion mutants; E, 1–501 and 1–650 truncation mutants; F, 1–869 truncation mutant; and G, triple mutants L760A/D761A/I762A (MT1) and W790A/S791A/S792A (MT2) were incubated with a splayed arm DNA substrate and ATPase activity was measured. A representative experiment (of at least two replicates) is shown for each mutant.
Likewise, C-terminal deletion constructs containing only the ATPase domain (ZRANB3 1–501) or the ATPase domain, PIP and NZF motifs (ZRANB3 1–650) were also inactive (Fig. 2E). However, a protein consisting of amino acids 1–869 was as active as the wild type protein (Fig. 2F). In all cases, the active proteins required DNA for ATP hydrolysis. Thus, the ZRANB3 ATPase domain requires an accessory domain that likely includes amino acids 721–869 for activity.

Amino acids 720–869 contain most, but not all, of the residues previously described to make-up the HARP-like domain. It is relatively highly evolutionarily conserved compared with flanking regions of ZRANB3 (Fig. 3). However, our sequence alignment failed to detect significant similarity with the HARP domains of SMARCAL1. We also compared the known secondary structure of the HARP domain to the predicted secondary structure of this ZRANB3 region. While there is some sim-
ilarity, the ZRANB3 domain contains a large insertion that is predicted to be α-helical. Mutations in highly conserved amino acids within this helix and in other highly conserved amino acids in this region (MT1: L760A/D761A/I762A and MT2: W790A/S791A/S792A) inactivate the protein (Fig. 2G). These data confirm that this region is necessary for DNA-dependent ATPase activity. Based on this data as well as additional information (see below) we designate amino acids 720–869 of ZRANB3 as a substrate recognition domain (SRD).

The ZRANB3 SRD Is Sufficient to Impart DNA Binding, ATPase, and Fork Remodeling Activities to the ATPase Domain—Since the ZRANB3 ATPase domain by itself is not active, we tested whether addition of the SRD via a flexible linker (Fig. 4A) is sufficient to impart DNA-dependent activity. Indeed, ZRANB3 1–501~720–869 is active in the presence of DNA although its activity is modestly decreased compared with wild-type ZRANB3 (Fig. 4B and C). Consistent with its DNA-dependent ATPase activity, ZRANB3 1–501~720–869 is capable of binding complex DNA substrates that mimic a replication fork (Fig. 4D). Similar to WT ZRANB3, ZRANB3 1–501~720–869 also catalyzes fork regression and fork restoration reactions, whereas an ATPase-deficient mutant (K163D) is inactive in these assays (Fig. 4E and F).

Incorporation of the MT1 mutations into this minimal enzymatic unit (1–501~720–869-MT1) inactivates its ATPase, DNA binding, and fork remodeling activities (Fig. 5). Thus, we conclude that amino acids 720–869 of ZRANB3 encode a SRD that is necessary and sufficient to impart DNA binding, ATPase and in vitro fork remodeling activities onto the ZRANB3 motor domain. Furthermore, this analysis defines the minimal enzymatic unit of ZRANB3 capable of catalyzing fork remodeling as containing amino acids 1–501 and 720–869.

The ZRANB3 SRD Is Required for Structure-specific Endonuclease Activity—In addition to catalyzing fork remodeling reactions, ZRANB3 was reported to act as an ATP-dependent, structure-specific endonuclease that nicks the duplex DNA of a splayed arm substrate (29). Endonuclease activity required both the HNH and ATPase domains (29). Thus, we hypothesized that the SRD domain of ZRANB3 may also be required for its nuclease activity. Indeed, mutations in the SRD inactivate nuclease activity (Fig. 6).

The ZRANB3 SRD Binds DNA—To test if amino acids 720–869 in ZRANB3 actually contain a DNA binding domain, we purified recombinant GST–720–869 from E. coli (Fig. 7A). Like full-length ZRANB3, GST–720–869 is not capable of binding either single-stranded or double-stranded DNA (Fig. 7B). However it can bind a splayed arm substrate, albeit with reduced affinity compared with full-length ZRANB3 (Fig. 7, C and D). Incorporating the MT1 mutations into either GST–720–869 or full-length ZRANB3 greatly reduced their ability to bind the splayed arm DNA substrate (Fig. 7, C and D).

Overall these results indicate that ZRANB3 amino acids 720–869 contains a domain that is both necessary and sufficient to impart substrate-selective DNA binding and enzymatic activity to the ZRANB3 ATPase domain. Thus, it acts as a SRD similar to the HARP domain of SMARCAL1 and the HIRAN domain of HLTF.

Discussion
In this study, we identified a structure recognition domain (SRD) in ZRANB3 that binds branched DNA substrates and confers DNA-dependent ATPase and fork remodeling activity to its SNF2-type motor domain. The SRD is also required for structure-specific endonuclease activity. A minimal enzymatic unit, containing only the SRD and the SNF2 ATPase domains,
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The high-resolution structures of the SRDs of HLTF and SMARCAL1 (HIRAN and HARP domains respectively) have been determined by x-ray crystallography (19–21). The HIRAN domain structure includes DNA, and explains its binding preference for duplex DNA with a short 3′ single-stranded DNA overhang (19). The HARP domain structure did not include DNA, but it resembles domains in other proteins that bind distorted DNA structures (20). SMARCAL1 prefers to bind DNA structures that contain at least five nucleotides of ssDNA (4), and point mutants in the HARP2 domain impair the binding preference for duplex DNA with a short 3′ single-stranded DNA overhang (19). Whether the HARP domain recognizes DNA structures without this region and also lacks DNA-dependent ATPase activity. Also, we found that mutations in the SRD inactivated ZRANB3 endonuclease activity as would be predicted if the SRD were required for DNA binding. We do not know why Yuan and colleagues were able to observe both DNA binding and ATPase activity in their mutant protein; however, we note that other mammalian DNA-dependent ATPases could have contaminated their protein purifications.

This study extends our understanding of how ZRANB3 operates as a fork remodeling enzyme and determines the necessary components to carry out its enzymatic activities. Future high-resolution structural analyses of the ZRANB3 and SMARCAL1...
proteins bound to DNA will be useful to better understand how their SRDs provide specificity to their fork remodeling activities.

Author Contributions—A. B. N. and D. C. designed the study and interpreted results. A. B. N. performed most experiments and A. C. M. and B. F. E. assisted with the DNA binding studies of the ZRANB3 SRD. A. B. N. and D. C. wrote the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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