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Structural and Biochemical Characterization of an Archaeal XPB: A Helicase Adapted For Damaged DNA Unwinding. Li Fan, Andrew Arvai, Priscilla K. Cooper, Shigenori Iwai, Fumio Hanaoka, John A. Tainer, Dept. of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037 USA.

The human xeroderma pigmentosum group B (XPB) helicase is essential for transcription, nucleotide excision repair, and TFIIH functional assembly. Here we determined crystal structures of an *Archaeoglobus fulgidus* XPB homolog (AfXPB) that characterize two RecA-like XPB helicase domains and discover a DNA damage recognition domain (DRD), a unique RED motif, a flexible thumb motif (ThM), and implied conformational changes within a conserved functional core. RED motif mutations dramatically reduce helicase activity, and the DRD and ThM, which flank the RED motif, appear structurally as well as functionally analogous to the MutS mismatch recognition and DNA polymerase thumb domains. Substrate specificity is altered by DNA damage, such that AfXPB unwinds dsDNA with 3' extensions but not blunt-ended dsDNA, unless it contains a lesion, as shown for CPD or (6-4) photoproducts. Together these results provide an unexpected mechanism of DNA unwinding with implications for XPB damage verification in nucleotide excision repair.