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Evidence for conformational capture mechanism for damage recognition by NER protein XPC/Rad4.[1] SAGNIK CHAKRABORTY, Univ of Illinois-Chicago, PETER J. STEINBACH, National Institutes of Health, DEBAMITA PAUL, JUNG-HYUN MIN, ANJUM ANSARI, Univ of Illinois-Chicago — Altered flexibility of damaged DNA sites is considered to play an important role in damage recognition by DNA repair proteins. Characterizing lesion-induced DNA dynamics has remained a challenge. We have combined ps-resolved fluorescence lifetime measurements with cytosine analog FRET pair uniquely sensitive to local unwinding/twisting to analyze DNA conformational distributions. This innovative approach maps out with unprecedented sensitivity the alternative conformations accessible to a series of DNA constructs containing 3-base-pair mismatch, suitable model lesions for the DNA repair protein xeroderma pigmentosum C (XPC) complex. XPC initiates eukaryotic nucleotide excision repair by recognizing various DNA lesions primarily through DNA deformability. Structural studies show that Rad4 (yeast ortholog of XPC) unwinds DNA at the lesion site and flips out two nucleotide pairs. Our results elucidate a broad range of conformations accessible to mismatched DNA even in the absence of the protein. Notably, the most severely distorted conformations share remarkable resemblance to the deformed conformation seen in the crystal structure of the Rad4-bound "recognition" complex supporting for the first time a possible "conformational capture" mechanism for damage recognition by XPC/Rad4.

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