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Structures of AlkA:DNA Complexes in Search Mode. D.A. Lehtinen, T Hollis, The Center for Structural Biology, Dept. of Biochemistry, Wake Forest Univ. Health Sciences, Winston-Salem, NC 27157, USA

The *Escherichia coli* 3-methyladenine glycosylase, AlkA, is a base excision repair (BER) enzyme that repairs alkylated damaged DNA using a base-flipping mechanism that exposes the damaged nucleotide allowing hydrolysis of the glycosylic bond. AlkA contains a versatile active site that successfully removes a wide range of alkylated bases, cyclic adducts and deaminated bases. In order to address how AlkA selectively recognizes and excises such chemically diverse damaged DNA from the vast excess of normal DNA, crystal structures were determined of AlkA bound to DNA containing a T:T mismatch and DNA containing 1, N⁶-ethenoadenine. The double-stranded DNAs were designed to represent weak substrates in attempts to capture the DNA bound at different stages of the catalytic reaction. These AlkA-DNA structures revealed non-specific DNA binding that is dramatically different from the previously solved AlkA-DNA structure where the DNA was bound at the active site. The new AlkA:DNA structures, together with the previously identified structure, support two different modes of AlkA-DNA binding, one in catalytic mode and one in search mode. We propose that in search mode the DNA is bound non-specifically, thus allowing the AlkA enzyme to scan along the DNA searching for damaged bases.