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Crystal Structures of Catalytic Complexes of the Oxidative DNA/RNA Repair Enzyme AlkB. B. Yu and J.F. Hunt, Department of Biological Sciences, Columbia University, NY, NY 10027 USA.

The most widely used chemotherapeutic drugs for the treatment of cancer are alkylating agents that create DNA lesions resulting in cell death. However, the efficacy of these agents is limited by their cytotoxicity to healthy tissues, and a number of serious side-effects are associated with their use. While endogenous DNA repair mechanisms help protect healthy cells, they also lead to drug resistance. AlkB is a protein whose role in DNA repair has only recently been elucidated. Identified as a member of the 2-oxoglutarate-Fe(II)-dependant dioxygenase superfamily, AlkB directly converts Sn2-alkylated DNA and RNA bases back into their original form. We have determined crystal structures of substrate and product complexes of *E. coli* AlkB at resolutions from 1.5 to 2.3 Å. Whereas the dioxygenase core matches that in other superfamily members, a unique subdomain holds methylated trinucleotide substrates into the active site through contacts to the polynucleotide backbone. Exposing crystals of the anaerobic Michaelis complex to air yields slow but substantial oxidation of 2-oxoglutarate that is inefficiently coupled to nucleotide oxidation. Ongoing work describing the binding of different nucleotide substrates will be presented.

