Roles for 4Fe-4S Clusters in the Repair of Damaged DNA Bases

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Damage-specific DNA glycosylases play an important role in detecting and removing damaged DNA bases as the first step in the base excision repair (BER) pathway. Studies of the BER glycosylase endonuclease III (endo III) indicated that it contained a 4Fe-4S cluster that was resistant to both oxidation and reduction, and therefore endo III is often used as an example of a non-redox active, structural 4Fe-4S-containing protein [1]. There are now a plethora of BER glycosylases that have been found to contain a 4Fe-4S cluster that may be grouped into two distinct classes [1]. Our laboratory has focused primarily on one enzyme from each class. *E. coli* MutY is a member of the "endo III-like" family and plays an important role in preventing mutations by removal of adenine from A:OG (where OG = 7,8-dihydro-8-oxo-2'-deoxyguanosine) mismatches in duplex DNA. The uracil DNA glycosylase (UDG) from *Archaeoglobus fulgidus* (AfUDG) is a member of a new family of uracil-removing glycosylases that is unrelated in both sequence and structure to the endo III-like family.

Structural studies of MutY identified an iron-sulfur cluster loop (FCL) that appears nicely positioned for interactions with DNA. We have found that modifications of amino acids within and around the FCL of MutY have a significant affect on damaged DNA binding and adenine excision. These studies have suggested that the 4Fe-4S cluster of MutY plays an important role in orienting residues of the FCL for interaction with DNA that allows for stabilization of a distorted DNA conformation needed for catalysis. Alterations of the cysteine ligands to the iron-sulfur cluster of AfUDG also suggest that the region supported by the cluster plays an intimate role in damage recognition and removal.

The close proximity of the cluster to DNA suggested that DNA binding may modulate the redox properties of the cluster. Indeed, electrochemical studies of MutY and AfUDG bound to DNA-modified gold electrodes demonstrate that the $[4Fe\text{-}4S]^{2+}$ cluster can participate in a DNA-mediated redox reaction, with a measured potential resembling that of a HIPIP ferredoxin. Recently, we have also observed that guanine radicals formed by guanine oxidation may be reduced (and therefore "repaired") by oxidation of the $[4Fe\text{-}4S]^{2+}$ cluster of MutY, suggesting that these metal sites may be able to directly facilitate DNA repair [2]. Taken together, the accumulating evidence indicates that the $[4Fe\text{-}4S]^{2+}$ cluster in these proteins is quite unusual and plays critical roles in the DNA repair activity of these enzymes.

1. Lukianova OL, David SS, *Curr. Opin. Chem. Biol.* 2005, **9**, *in press*.
2. Yavin E, Boal AK, Stemp EDA, Boon EM, Livingston AL, O'Shea VL, David SS, Barton JK, *Proc. Natl. Acad. Sci. USA* 2005, **102**, 3546-3551.