DNA-mediated Charge Transport in DNA Repair

Jacqueline K. Barton

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena CA 91125

[4Fe-4S] clusters are ubiquitous to base excision repair enzymes, yet a role for this cofactor has been elusive. We have found that, bound to DNA, these repair enzymes, notably MutY and Endo III from *Escherichia coli,* become redox-active. Electrochemistry on DNA-modified electrodes shows that binding to DNA shifts the redox potential of the $[4Fe\text{-}4S]^{3+/2+}$ couple to the range characteristic of high potential iron proteins and activates the proteins towards oxidation. In EPR experiments at 10K, redox activation upon DNA binding is also evident to yield the oxidized $[4Fe\text{-}4S]^{3+}$ cluster and the partially degraded $[3Fe\text{-}4S]^{1+}$ cluster. Based upon this DNA-dependent redox activity, we propose a model for the rapid detection of DNA lesions using DNA-mediated electron transfer among the base excision repair enzymes. Redox activation upon DNA binding and charge transfer through well-matched DNA to an alternate bound repair protein can lead to the rapid redistribution of proteins onto genome sites in the vicinity of DNA lesions. This redox activation furthermore establishes a functional role for the ubiquitous [4Fe-4S] clusters in DNA repair enzymes that involves redox chemistry and provides a means to consider DNA-mediated signaling within the cell.