Redox signaling between DNA repair proteins for efficient lesion detection

Amie K. Boal[a], Joseph C. Genereux[a], Pamela A. Sontz[a], Jeffrey A. Gralnick[b], Dianne K. Newman[c,1] and Jacqueline K. Barton[a,1]

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

[b]Department of Microbiology, BioTechnology Institute, University of Minnesota, St. Paul, NM 55108

[c]Departments of Biology and Earth, Atmospheric and Planetary Science, and Howar Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA 02139

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Abstract

Base excision repair (BER) enzymes maintain the integrity of the genome, and in humans, BER mutations are associated with cancer. Given the remarkable sensitivity of DNA-mediated charge transport (CT) to mismatched and damaged base pairs, we have proposed that DNA repair glycosylases (EndoIII and MutY) containing a redox-active [4Fe4S] cluster could use DNA CT in signaling one another to search cooperatively for damage in the genome. Here, we examine this model, where we estimate that electron transfers over a few hundred base pairs are sufficient for rapid interrogation of the full genome. Using atomic force microscopy, we found a redistribution of repair proteins onto DNA strands containing a single base mismatch, consistent with our model for CT scanning. We also demonstrated in Escherichia coli a cooperativity between EndoIII and MutY that is predicted by the CT scanning model. This relationship does not require the enzymatic activity of the glycosylase. Y82A EndoIII, a mutation that renders the protein deficient in DNA-mediated CT, however, inhibits cooperativity between MutY and EndoIII. These results illustrate how repair proteins might efficiently locate DNA lesions and point to a biological role for DNA-mediated CT within the cell.