Protein–DNA charge transport: Redox activation of a DNA repair protein by guanine radical

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DNA charge transport (CT) chemistry provides a route to carry out oxidative DNA damage from a distance in a reaction that is sensitive to DNA mismatches and lesions. Here, DNA-mediated CT also leads to oxidation of a DNA-bound base excision repair enzyme, MutY. DNA-bound Ru(III), generated through a flash/quench technique, is found to promote oxidation of the $[4Fe\text{-}4S]^{2+}$ cluster of MutY to $[4Fe\text{-}4S]^{3+}$ and its decomposition product $[3Fe\text{-}4S]^{1+}$. Flash/quench experiments monitored by EPR spectroscopy reveal spectra with g = 2.08, 2.06, and 2.02, characteristic of the oxidized clusters. Transient absorption spectra of poly(dGC) and $[Ru(phen)_2dppz]^{3+}$ (dppz = dipyridophenazine), generated *in situ*, show an absorption characteristic of the guanine radical that is depleted in the presence of MutY with formation instead of a long-lived species with an absorption at 405 nm; we attribute this absorption also to formation of the oxidized $[4Fe\text{-}4S]^{3+}$ and $[3Fe\text{-}4S]^{1+}$ clusters. In ruthenium-tethered DNA assemblies, oxidative damage to the 5'-G of a 5'-GG-3' doublet is generated from a distance but this irreversible damage is inhibited by MutY and instead EPR experiments reveal cluster oxidation. With ruthenium-tethered assemblies containing duplex versus single-stranded regions, MutY oxidation is found to be mediated by the DNA duplex, with guanine radical as an intermediate oxidant; guanine radical formation facilitates MutY oxidation. A model is proposed for the redox activation of DNA repair proteins through DNA CT, with guanine radicals, the first product under oxidative stress, in oxidizing the DNA-bound repair proteins, providing the signal to stimulate DNA repair.

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