A role for DNA-mediated charge transport in regulating p53: Oxidation of the DNA-bound protein from a distance

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Abstract

Charge transport (CT) through the DNA base pairs provides a means to promote redox reactions at a remote site and potentially to effect signaling between molecules bound to DNA. Here we describe the oxidation of a cell-cycle regulatory protein, p53, from a distance through DNA-mediated CT. A consensus p53 binding site as well as three DNA promoters regulated by p53 were synthesized containing a tethered DNA photooxidant, anthraquinone. Photoinduced oxidation of the protein occurs from a distance; introduction of an intervening CA mismatch, which inhibits DNA-mediated CT, prevents oxidation of p53. DNA-mediated oxidation is shown to promote dissociation of p53 from only some promoters, and this sequence-selectivity in oxidative dissociation correlates with the biological regulation of p53. Under severe oxidative stress, effected here through oxidation at long range, p53 dissociates from a promoter that activates DNA repair as well as the promoter for the negative regulator of p53, Mdm2, but not from a promoter activating cell-cycle arrest. Mass spectrometry results are consistent with disulfide bond formation in p53 upon DNA-mediated oxidation. Furthermore, DNA-bound p53 oxidation is shown *in vivo* by up-regulation of p53 and subsequent irradiation in the presence of a rhodium photooxidant to give a new p53 adduct that can be reversed with thiol treatment. This DNA-mediated oxidation of p53 parallels that seen by treating cells with hydrogen peroxide. These results indicate a unique mechanism using DNA-mediated CT chemistry by which p53 activity on different promoters may be controlled globally under conditions of oxidative stress.