Oxidation by DNA Charge Transport Damages Conserved Sequence Block II, a Regulatory Element in Mitochondrial DNA†

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Abstract:

Sites of oxidative damage in mitochondrial DNA have been identified on the basis of DNA-mediated charge transport. Our goal is to understand which sites in mitochondrial DNA are prone to oxidation at long range and whether such oxidative damage correlates with cancerous transformation. Here we show that a primer extension reaction can be used to monitor directly oxidative damage to authentic mitochondrial DNA through photoreactions with a rhodium intercalator. The complex $[Rh(phi)_2bpy]Cl_3$ (phi = 9,10-phenanthrenequinone diimine) binds to DNA without sequence specificity and, upon photoactivation, either promotes strand breaks directly at the binding site or promotes one-electron oxidative damage; comparing the sites of base oxidation to direct strand breaks reveals the oxidative damage that arises from a distance through DNA-mediated charge transport. Significantly, base oxidation by charge transport overlaps with known mutational hot spots associated with cancers at nucleotides surrounding positions 263 and 303; the latter is known as conserved sequence block II and is vital to DNA replication. Since DNA base oxidation at conserved sequence block II should weaken the ability of damaged mitochondrial genomes to be replicated, DNA-mediated charge transport may provide a protection mechanism for excluding damaged DNA.