Common Mitochondrial DNA Mutations Generated through DNA-Mediated Charge Transport

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Mutation sites that arise in human mitochondrial DNA as a result of oxidation by a rhodium photooxidant have been identified. HeLa cells were incubated with $[Rh(phi)_2bpy]Cl_3$ (phi is 9,10-phenanthrenequinone diimine), an intercalating photooxidant, to allow the complex to enter the cell and bind mitochondrial DNA. Photoexcitation of DNA-bound $[Rh(phi)_2bpy]^{3+}$ can promote the oxidation of guanine from a distance through DNA-mediated charge transport. After two rounds of photolysis and growth of cells incubated with the rhodium complex, DNA mutations in a portion of the mitochondrial genome were assessed via manual sequencing. The mutational pattern is consistent with dG to dT transversions in the repetitive guanine tracts. Significantly, the mutational pattern found overlaps oxidative damage hot spots seen previously. These mutations are found within conserved sequence block II, a critical regulatory element involved in DNA replication, and these have been identified as sites of low oxidation potential to which oxidative damage is funneled. On the basis of this mutational analysis and its correspondence to sites of long-range oxidative damage, we infer a critical role for DNA charge transport in generating these mutations and, thus, in regulating mitochondrial DNA replication under oxidative stress.

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