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THE MISMATCH REPAIR SYSTEM PROTECTS CELLS FROM GENOTOXIN-INDUCED
CC→TT BASE PAIR SUBSTITUTIONS

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Exposure to environmental genotoxins gives rise to specific DNA mutations. Several toxins, such as hydrogen peroxide, the alkylating agent EMS, and ultraviolet C light, yield G:C → A:T mutations in wild type cells. In contrast, when the highly reactive hydroxyl radical is generated with hydrogen peroxide plus copper and iron, CC → TT mutations are observed. However, the induction frequencies for the CC → TT mutations are very low in wild type cells. To better characterize the induction of CC → TT mutations we repeated all experiments in mismatch repair (PMS2)-deficient cells and again observed the induction of CC → TT mutations with hydrogen peroxide and metals, but at a frequency approximately 40-fold higher than in wild type cells. Moreover, dissimilar from wild type cells, most mutations induced by UV C in the mismatch repair deficient cells were also tandem CC → TT substitutions. These results begin the process of characterizing the mutational spectra specific to both wild type and mismatch repair deficient mouse kidney cells when exposed to a plethora of genotoxins in a reversion assay designed to detect both C→T and CC → TT mutations. It is concluded that the mismatch repair system is necessary to protect cells from the formation of tandem CC → TT mutations.