Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells.

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Abstract

We have previously shown that 4-quinolone drugs cause a selective loss of mitochondrial DNA (mtDNA) from mouse L1210 leukemia cells. The loss in mtDNA was associated with a delayed loss in mitochondrial function. Here, we report that the 4-quinolone drug ciprofloxacin is cytotoxic to a variety of cultured mammalian cell lines at concentrations that deplete cells of mtDNA. The IC50 values for ciprofloxacin varied from 40 to 80 micrograms/ml depending on the cell line tested. Cytotoxicity required continuous exposure of cells to drug for 2-4 days, which corresponded to approximately three or four cell doublings. Shorter times of drug exposure did not cause significant cytotoxicity. In addition, cells became drug resistant when they were grown under conditions that bypassed the need for mitochondrial respiration. Resistance was not due to a decrease in cellular drug accumulation, suggesting that ciprofloxacin cytotoxicity is caused by the loss of mtDNA-encoded functions. Analysis of mtDNA from ciprofloxacin-treated cells revealed the presence of site-specific, double-stranded DNA breaks. Furthermore, exonuclease protection studies indicated that the 5'-, but not the 3'-, ends of the drug-induced DNA breaks were tightly associated with protein. These results suggest that ciprofloxacin may be causing cytotoxicity by interfering with a mitochondrial topoisomerase II-like activity, resulting in a loss of mtDNA.

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