The endoperoxide ascaridol shows strong differential cytotoxicity in nucleotide excision repair-deficient cells.


Source

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Abstract

Targeting synthetic lethality in DNA repair pathways has become a promising anti-cancer strategy. However little is known about such interactions with regard to the nucleotide excision repair (NER) pathway. Therefore, cell lines with a defect in the NER genes ERCC6 or XPC and their normal counterparts were screened with 53 chemically defined phytochemicals isolated from plants used in traditional Chinese medicine for differential cytotoxic effects. The screening revealed 12 drugs that killed NER-deficient cells more efficiently than proficient cells. Five drugs were further analyzed for IC(50) values, effects on cell cycle distribution, and induction of DNA damage. Ascaridol was the most effective compound with a difference of >1000-fold in resistance between normal and NER-deficient cells (IC(50) values for cells with deficiency in ERCC6: 0.15µM, XPC: 0.18µM, and normal cells: >180µM). NER-deficiency combined with ascaridol treatment led to G2/M-phase arrest, an increased percentage of subG1 cells, and a substantially higher DNA damage induction. These results were confirmed in a second set of NER-deficient and proficient cell lines with isogenic background. Finally, ascaridol was characterized for its ability to generate oxidative DNA damage. The drug led to a dose-dependent increase in intracellular levels of reactive oxygen species at cytotoxic concentrations, but only NER-deficient cells showed a strongly induced amount of 8-oxodG sites. In summary, ascaridol is a cytotoxic and DNA-damaging compound which generates intracellular reactive oxidative intermediates and which selectively affects NER-deficient cells. This could provide a new therapeutic option to treat cancer cells with mutations in NER genes.

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PMID:22280988