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Guanidine-reactive agent phenylglyoxal induces DNA damage and cancer cell death

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Abstract:
Background: DNA-damaging compounds (e.g., alkylating agents, cytotoxic antibiotics and DNA topoisomerase poisons) are the most widely used anticancer drugs. The inability of tumor cells to properly repair some types of DNA damage may explain why specific DNA-damaging drugs can selectively kill tumor cells. Phenylglyoxal is a dicarbonyl compound known to react with guanidine groups such as that of the DNA base guanine, therefore suggesting that phenylglyoxal could induce DNA damage and have anticancer activity.
Methods: Cellular DNA damage was measured by the alkaline comet assay and the γH2AX focus assay. Formation of topoisomerase I- and topoisomerase II-DNA complexes was assessed by the TARDIS assay, an immunofluorescence technique that employs specific antibodies to DNA topo I or topo II to detect the protein covalently bound to the DNA in individual cells. Cell growth inhibition and cytotoxicity were determined by XTT, MTT and clonogenic assays. Apoptosis was assessed by the Annexin V flow cytometry assay.
Results: Phenylglyoxal induced cellular DNA damage and formation of high levels of topoisomerase I- and topoisomerase II-DNA complexes in cells. These topoisomerase-DNA complexes were abolished by catalase pretreatment and correlated well with the induction of apoptosis. Phenylglyoxal-induced cell death was partially prevented by catalase pretreatment and was higher in lung cancer cells (A549) than in normal lung fibroblasts (MRC5). Mammalian cell lines defective in nucleotide excision repair (NER), homologous recombination (HR) and non-homologous end joining (NHEJ) were more sensitive to phenylglyoxal than parental cells; this suggests that phenylglyoxal may induce bulky distortions in the shape of the DNA double helix (which are repaired by the NER pathway) and DNA double-strand breaks (which are repaired by HR and NHEJ).
Conclusion: This report shows that phenylglyoxal is a new DNA-damaging agent with anticancer activity, and suggests that tumor cells with defects in NER, HR and NHEJ may be hypersensitive to the cytotoxic activity of phenylglyoxal.

Key words:
DNA damage response, DNA topoisomerases, nucleotide excision repair, non-homologous end joining, homologous recombination

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