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Mechanism of radioprotection by dihydroxy-1-selenolane (DHS): Effect of fatty acid conjugation and role of glutathione peroxidase (GPx)

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Abstract

Dihydroxy-1-selenolane (DHS) previously reported to exhibit radioprotective activity was investigated to understand its mechanism of action in CHO cells of epithelial origin. DHS pre-treatment at 25 μ M for 16 h significantly protected CHO cells from radiation (4-11 Gy)-induced delayed mitotic cell death. Further to examine, how increased cellular uptake can influence this mechanism, studies have been performed with DHS-C₆, a lipophilic conjugate of DHS. Accordingly CHO cells pre-treated with DHS-C₆, showed increased survival against radiation exposure. Notably treatment with both DHS and DHS-C₆ significantly increased glutathione peroxidase (GPx) activity in cells by ~ 2.5 fold. Additionally, the compound DHS or DHS-C₆ led to faster repair of DNA in irradiated cells and subsequently inhibited the G2/M arrest. Anticipating the role of GPx in radioprotection, our investigations revealed that addition of mercaptosuccinic acid, a pharmacological inhibitor of GPx reversed all the above effects of DHS or DHS-C₆. Further inhibitors of check point kinase 1 (CHK1) and DNA-protein kinase (DNA-PK) although abrogated the radioprotective effect of DHS or DHS-C₆ separately, did not show additive effect in combination with GPx inhibitor, suggesting their cross talk. In contrast to these results, both DHS and DHS-C₆ treatment did not protect spleen lymphocytes from the radiation-induced apoptosis. Thus results confirmed that both DHS and DHS-C₆ protected cells from radiation-induced mitotic death by augmenting DNA repair in a GPx dependant manner.

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