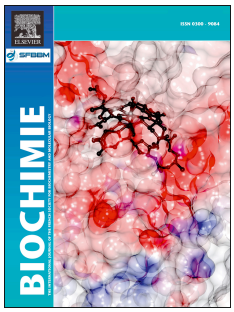
Accepted Manuscript



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

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PII: S0300-9084(17)30273-0

DOI: 10.1016/j.biochi.2017.10.021

Reference: BIOCHI 5302

To appear in: *Biochimie*

Received Date: 23 June 2017

Accepted Date: 25 October 2017

Please cite this article as: P. Verma, A. Kunwar, K. Arai, M. Iwaoka, K.I. Priyadarsini, Mechanism of radioprotection by dihydroxy-1-selenolane (DHS): Effect of fatty acid conjugation and role of glutathione peroxidase (GPx), *Biochimie* (2017), doi: 10.1016/j.biochi.2017.10.021.

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 µM 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-C_6, a lipophilic conjugate of DHS. Accordingly CHO cells pre-treated with DHS-C_6, showed increased survival against radiation exposure. Notably treatment with both DHS and DHS-C_6 significantly increased glutathione peroxidase (GPx) activity in cells by ~ 2.5 fold. Additionally, the compound DHS or DHS-C_6 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-C_6. Further inhibitors of check point kinase 1 (CHK1) and DNA-protein kinase (DNA-PK) although abrogated the radioprotective effect of DHS or DHS-C_6 separately, did not show additive effect in combination with GPx inhibitor, suggesting their cross talk. In contrast to these results, both DHS and DHS-C_6 treatment did not protect spleen lymphocytes from the radiation-induced apoptosis. Thus results confirmed that both DHS and DHS-C_6 protected cells from radiation-induced mitotic death by augmenting DNA repair in a GPx dependant manner.