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Novel benzoxazine radiosensitizers and their mechanism of action in cancer cells

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Discovery and development of novel small molecule inhibitors of enzymes involved in the repair of DNA double stranded breaks (DSB) induced by radiation is currently a major research field. The DNAdependant protein kinase (DNA-PK) enzyme plays a major part in the repair of DSB's and hence in the radio-resistance of tumour cells. Inhibitors of DNA-PK have been tested successfully in the past for their ability to sensitize cancer cells to the effects of radiation. Here we present a series of novel benzoxazines and analyse their ability to cause sensitization of a variety of cancer cell lines to radiation. Cancer cell lines used in this study were a cervical cancer (HeLa), colorectal adenocarcinoma (HT29) and lung carcinoma (A549). Assays used were the clonogenic survival assay, the H2AX assay for DSB'sa flow cytometric assay for hypodiploidy as a measure of apoptosis, and assays for phosphorylated DNA-PK by both flow cytometry, and western blotting. There was a significant reduction in survival rate of cell lines after treating them concomitantly with both radiation and three of our compounds. Quantification of H2AX phosphorylation indicated the existence of DSB's the repair of which was found to be delayed significantly for at least 24 hrs. post-irradiation. There was a significant increase in the percentage of cells in SubG1 phase indicating an increased proportion of cells entering apoptosis. There was also a significant reduction in the phosphorylation of DNA-PK (s2056) when tested with some of our compounds. Our results reveal the effectiveness of selected, novel benzoxazines as promising radiosensitizing agents. The mechanism of action appears to be through inhibition of DNA-PK leading to delayed DNA repair, cell cycle arrest and apoptosis.

Keywords: DNA-PK, Benzoxazines, radiosensitizing, apoptosis, gamma H2AX.