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NVP-AUY922 and NVP-BEP800 selectively radiosensitize tumor cell lines but not normal skin fibroblasts

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In previous studies we have described the radiosensitizing potential of novel heat shock protein 90 (Hsp90) inhibitors NVP-AUY922 and NVP-BEP800 in normoxic and hypoxic conditions (Stingl et al. 2010, Djuzenova et al. 2012). However, the therapeutic potential of Hsp90 inhibitor as a radiation sensitizer will strongly depend on a selective increase in the radiosensitivity of tumor cells over normal cells. In present study we examined the impact of NVP-AUY922 and NVP-BEP800 on radiation response of two normal fibroblast cell lines HFib1 and HFib2 compared with the two established tumor cell lines (A549 and SNB19).
The cell lines tested were treated with Hsp90 inhibitor (200 nM) 1 hour before IR, irradiated in the drug-containing medium and kept thereafter up to 48 h after irradiation. Thirty minutes, 24 h and 48 h after drug-IR treatment cells were plated in Petri dishes for the colony survival assay. Furthermore we determined the expression of Hsp90 and its clients, several survival (Akt, Raf-1, survivin etc.) and cell cycle associated (Cdk1, Cdk4 and pRb) proteins.
Interestingly, we found that Hsp90 inhibitors NVP-AUY922 and NVP-BEP800 did not radiosensitize the both tested fibroblast lines (HFib1 and HFib2) if inhibitors are kept in culture medium for 30 min and 24 h post-IR. An extended exposure (48 h) of irradiated fibroblasts to NVP-AUY922 sensitizes them to radiation, however, to a much lesser extent than that was observed in case of tumor cells. Moreover, the prolonged incubation of normal fibroblasts with the Hsp90 inhibitors did not affect their plating efficiency indicating that Hsp90 inhibitors were not toxic to normal tissue. This conclusion can be supported by the comparison of D10 values 48h post-IR, which decreased after treatment with NVP-AUY922 from 8 to 3.9 Gy for SNB19 cells, whereas in HFib1 and HFib2 from 6.5 to ~5.5 Gy. Further finding of the study is the fact that Hsp90 inhibition and IR up-regulated the expression of Hsp90 and Hsp70, but to much lesser level than that in tumor cell lines A549 and SNB19. The expression of several other marker proteins in normal fibroblasts after combined drug-IR was mostly similar to that in tumor cell lines.
To summarize, our data show that the Hsp90 inhibitors NVP-AUY922 and NVP-BEP800 can preferentially radiosensitize tumor cells, while affecting non-malignant cells to a much lesser extent.

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