Radiosensitization of normoxic and hypoxic h1339 lung tumor cells by heat shock protein 90 inhibition is independent of hypoxia inducible factor-1α.

Abstract:
Ionizing irradiation is a commonly accepted treatment modality for lung cancer patients. However, the clinical outcome is hampered by normal tissue toxicity and tumor hypoxia. Since tumors often have higher levels of active heat shock protein 90 (Hsp90) than normal tissues, targeting of Hsp90 might provide a promising strategy to sensitize tumors towards irradiation. Hsp90 client proteins include oncogenic signaling proteins, cell cycle activators, growth factor receptors and hypoxia inducible factor-1α (HIF-1α). Overexpression of HIF-1α is assumed to promote malignant transformation and tumor progression and thus might reduce the accessibility to radiotherapy. Herein, we describe the effects of the novel Hsp90 inhibitor NVP-AUY922 and 17-allylamino-17-demethoxygeldanamycin (17-AAG), as a control, on HIF-1α levels and radiosensitivity of lung carcinoma cells under normoxic and hypoxic conditions. NVP-AUY922 exhibited a similar biological activity to that of 17-AAG, but at only 1/10 of the dose. As expected, both inhibitors reduced basal and hypoxia-induced HIF-1α levels in EPLC-272H lung carcinoma cells. However, despite a down-regulation of HIF-1α upon Hsp90 inhibition, sensitivity towards irradiation remained unaltered in EPLC-272H cells under normoxic and hypoxic conditions. In contrast, treatment of H1339 lung carcinoma cells with NVP-AUY922 and 17-AAG...
resulted in a significant up-regulation of their initially high HIF-1α levels and a concomitant increase in radiosensitivity. In summary, our data show a HIF-1α-independent radiosensitization of normoxic and hypoxic H1339 lung cancer cells by Hsp90 inhibition.