Abstract

Overexpression of the hypoxia-inducible transcription factor 1α (HIF-1α) is a common characteristic trait of almost all solid tumors. HIF-1α has been identified as a driving force for tumor progression, metastatic spread and the occurrence of therapy resistance in a variety of tumors. HIF-1α appears to play a central role in the regulation of several DNA-repair pathways; however, the underlying molecular mechanisms are not fully understood so far. Therefore, the aim of the present study was the *in vitro* and *in vivo* characterization of HIF-1α's role in mediating radioresistance as well as the identification of potential underlying mechanisms. For this purpose, a functional inactivation of the regulatory α-subunit of HIF-1 (HIF-1α) in the HIF-2α deficient murine LLC cell line was established via lentiviral transduction with shRNA vectors. The assumed radioresistance promoting function of HIF-1α was supported by the analysis of different tumor-relevant aspects *in vitro*: the inactivation of HIF-1α significantly reduced proliferation, and eliminated most of the clonogenic potential of LLC cells. This effect was mainly due to a marked cell cycle arrest in G2/M after irradiation and a significantly impaired repair ability of DNA double strand breaks. In line with this, HIF-1α seems to functionally interact with several components of the DNA damage response pathway. Furthermore, the specific inactivation of HIF-1α significantly postponed tumor regrowth after irradiation in an allograft tumor model with a functional immune system. Taken together, the present study revealed that HIF-1α holds the potential of a therapeutic target since it influences therapy sensitivity of solid tumors. In consideration of these results, HIF-1α-inhibiting treatment strategies in combination with DNA-repair pathway inhibitors may significantly increase treatment efficiency and improve patients' prognosis.