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Inhibition of Heme Oxygenase-1 (HO-1) increases responsiveness of pancreatic cancer cells to anti-cancer treatment

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The heme oxygenase (HO) system catalyzes the rate-limiting step in the degradation of heme to produce equimolar quantities of biliverdin, CO and free iron. To date, three isoforms (HO-1, HO-2, HO-3) that catalyze this reaction have been identified. HO-1 is a 32kDa inducible heat shock protein, which is found at low levels in most mammalian tissues. But the expression of HO-1 is highly induced by a variety of stress-stimuli, including heat shock, UV irradiation, hydrogen peroxide, heavy metals, hypoxia, and cytokines. Furthermore HO-1 and its products were described to have potent cytoprotective properties, based on their anti-inflammatory and anti-apoptotic effects. Therefore, HO-1 may serve as a key biological molecule in the adaptation to defense against oxidative stress and cellular stress of other kinds.
Elevated HO-1 activity was found in several human tumors, such as renal carcinoma, prostate tumors and lymphosarcoma. In human gliomas and melanomas, HO-1 was shown to be a valid marker for macrophage infiltration and neovascularization. Upregulation of HO-1 gene is related to the enhanced expression of several angiogenic factors, such as IL-1 and IL-6, TNF-α and TGF-β. This evidence suggests that HO-1 could stimulate the tumor growth and metastasis formation by increase of the tumor vasculature. Indeed, a relationship between malignant tumor behavior and upregulation of HO-1 may exist as shown by ample of data. In several experimental solid tumor models, inhibition of HO-1 activity decreased tumor growth, by induction of apoptosis and/or inhibition of angiogenesis.
Pancreatic cancer has a very poor prognosis and high mortality rate. Surgical treatment of this malignancy is not always feasible even in patients with a limited disease. Available chemotherapy and radiotherapy regiments are not consistently effective in patients with advanced disease, thus overall 5 years survival from diagnosis is only about 5%. This clearly shows that novel treatment modalities, which take advantage of molecular mechanisms in cancerogenesis, are needed to improve the prognosis of these patients.
In this study we demonstrate that the cell specific down-regulation of HO-1 expression and activity sensitize pancreatic cancer cells to conventional anti-cancer treatment options.
The expression of HO-1 was analyzed in human pancreatic cancer samples in comparison to normal pancreas by quantitative PCR, Western blot and confocal microcopy. The influence of radio- and chemotherapy on HO-1 expression in pancreatic cancer cell lines was evaluated. Furthermore, HO-1 expression was specifically suppressed by siRNA transfection. Alterations of growth behavior and resistance to anti-cancer treatment were tested.
Human pancreatic cancer showed over-expression 6-fold and 3,5-fold of HO-1 expression in comparison to normal pancreas on mRNA and protein level, respectively ($p< 0.05$). The

cancer tissue revealed marked immunoreactivity in tumor cells and in tumor associated immunocytes. Treatment of the pancreatic cancer cell lines with Gemcitabine or radiation strongly induced endogenous HO-1 expression. Targeted knockdown of this HO-1 expression led to pronounced growth inhibition of the pancreatic cancer cells and made tumor cells significantly more sensitive to radio- and chemotherapy.
In conclusion, HO-1 seems to provide a growth advantage to pancreatic cancer cells and to make them resistant against radio- and chemotherapy. Specific inhibition of HO-1 sensitizes the tumor cells to anti-cancer treatment and may therefore be a new adjuvant agent in the therapy of pancreatic cancer.