Philipp Nuhn
Dr. med.

Hämoxygenase-1 und ihre Metaboliten im Pankreaskarzinom: Neue therapeutische Optionen durch Alteration der Tumorprogression

Geboren am 26.03.1981 in Bernkastel-Kues
Reifeprüfung am 09.06.2000 in Biesdorf/Eifel
Studiengang der Fachrichtung Medizin vom WS 2001/2002 bis SS 2007
Physikum am 02.09.2003 in Heidelberg
Klinisches Studium in Heidelberg
Praktisches Jahr in Hanover (Dartmouth College), Heidelberg, Zürich und New York (Cornell University)
Staatsexamen am 11.06.2008 an der Universität Heidelberg

Promotionsfach: Chirurgie
Doktorvater: Prof. Dr. med. Helmut Friess

Pancreatic cancer (PaCa) is a fatal human cancer due to its exceptional resistance to all current anticancer therapies. The cytoprotective enzyme heme oxygenase-1 (HO-1) is significantly overexpressed in PaCa and seems to play an important role in cancer resistance to anticancer treatment. The inhibition of HO-1 sensitized PaCa cells to chemo- and radiotherapy in vitro.
Therefore, we investigated the effects of HO-1 and its metabolites biliverdin, carbon monoxide and iron on pancreatic cancer cells.
PaCa cell lines with divergent HO-1 expression patterns were used in a murine orthotopic cancer model. HO-1 expression and activity was regulated by zinc (inhibition) and cobalt (induction) protoporphyrin. Furthermore, the influence of cellular HO-1 levels and its metabolites on effects of standard chemotherapy with gemcitabine was tested in vivo and in vitro.
High HO-1 expression in PaCa cell lines was associated with increased chemoresistance in vitro. Chemoresistance to gemcitabine was increased during HO-1 induction in PaCa cells expressing low levels of HO-1. The inhibition of HO-1 activity in pancreatic tumors with high

HO-1 boosted chemotherapeutic effects in vivo significantly. Furthermore, biliverdin and iron promoted PaCa resistance to chemotherapy. Consequently, specific iron chelation by desferrioxamine revealed profound anticancerous effects.

In summary, the inhibition of HO-1 and the chelation of iron in PaCa cells were associated with increased sensitivity and susceptibility of pancreatic tumors to chemotherapy in vivo. The metabolites biliverdin and iron seem to be involved in HO-1-mediated resistance to anticancer treatment. Therefore, HO-1 inhibition or direct interference with its metabolites may evolve new strategies in PaCa therapy.