Zhi Xiao
Dr.med.

The EGF receptor is involved in the development of multidrug resistance in experimental hepatocellular carcinoma

Promotionsfach: Chirurgie
Doktorvater: Prof. Dr. med. Peter Schemmer

Tyrosine kinases and ABC transport proteins are over expressed in hepatocellular cancer and correlate with reduced survival. Recently, an involvement of the EGF activated tyrosine-kinase pathway in the development of ABC transport protein mediated multidrug resistance has been discussed. The aim of this study was to systematically analyze the effects of tyrosine-kinase pathway activation on the multidrug resistance phenotype in hepatocellular cancer cells.
Multidrug resistance was analyzed in HepG2 and HuH7 cells. Expression and function of ABC transport proteins were evaluated by western blot, RT-PCR and rhodamine uptake assay. siRNA was used to inhibit the EGFR expression.
Chemotherapy significantly induced multidrug resistance genes expression in a dose dependent manner and increased ABC transport protein PGP and MRP2 expression in both HCC cell lines. Interestingly, cytostatic treatment significantly increased the mRNA expression of tyrosine kinases. The enhanced expression of the tyrosine kinase pathway by EGF up-regulated the ABC transport mRNA expression and increased the survival of resistant HCC cells. In contrast, inhibition of the EGFR by siRNA lead to significantly decreased drug resistance protein mRNA expression and reduced cellular survival in HepG2 cells. Combinative treatment with the specific EGFR inhibitor gefitinib restored the chemosensitivity of resistant HepG2 cells.
The EGF activated tyrosine kinase pathway is involved in the development and regulation of multidrug resistance in hepatocellular carcinoma. Inhibition of EGFR and restoration of chemosensitivity may improve the design of personalized targeted therapies in patients with highly resistant tumors.