2 ABSTRACT

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Expression of cytochrome P450 2C9 in hepatic tumors.

Diploma thesis

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Background: Liver cancer is a growing health problem worldwide. The most common primary hepatic malignancy is hepatocellular carcinoma (HCC). It is a multifactorial disease arising from multiple genetic and non-genetic alterations, most importantly viral infections and toxic injury (e.g. alcohol abuse). Cytochromes P450 (CYPs) participate on a plethora of metabolic processes in human body. Several CYPs play a role in tumorigenesis as well. This theses covers the topics of hepatic malignancies and regulation of cytochrome P450 expression to evaluate the possible relationship to the hepatocarcinogenesis and pharmacotherapy of HCC. In CYP2C9, which is one of the most important drug-metabolizing CYP forms, gene expression analysis was performed in HCC tumor and surrounding tissue, also including CYP2C9 major regulators – nuclear receptors PXR (pregnane-X-receptor) and CAR (constitutive androstane receptor).

Methods: Samples of hepatocellular carcinoma and surrounding non-cancerous tissue from 12 patients were obtained from the biobank of Masaryk Memorial Cancer Institute, Brno, Czech Republic. Gene expression of CYP2C9, CAR and PXR at the mRNA level was assessed using real-time PCR. Where there was a sufficient amount of tissue, protein analysis (immunoblotting) was performed to confirm the qPCR data.

Results: Expression CYP2C9 was half samples of tumor tissue is reduced by one to several orders of magnitude compared with the reference non-tumor tissue. In the other half of the cohort, CYP2C9 expression was similar to that in surrounding non-cancerous tissue. The expression was confirmed at the protein level and correlated with expression of nuclear receptors PXR and CAR and also with the tumor grade – tumors with grade 3-4 (less differentiated hepatic tissue) had significantly lower CYP2C9 expression.

Conclusions: The expression of CYP2C9 and nuclear receptor PXR and CAR in HCC tumor tissue is significantly reduced in about half of the patients and correlates with the histological grading of the tumor.