Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

SOX9 in the development and chemotherapy of cholangiocarcinoma

Autor: Xiaodong Yuan
Institut / Klinik: II. Medizinische Klinik
Doktorvater: Prof. Dr. S. Dooley

SOX9 is a critical transcription factor for liver embryogenesis, homeostasis and hepatocellular carcinoma (HCC) development. However, the oncogenic role of SOX9 has not been investigated in cholangiocarcinoma (CCA). As CCA is a devastating malignancy with limited treatment options, elucidation of its underlying mechanisms and identification of new molecular markers of tumorigenesis and progression of CCA is necessary for improving diagnosis and prognosis of this cancer type. This study aims at investigating the effects and underlying mechanisms of SOX9 in tumorigenesis and chemotherapy of CCA.

In this thesis, I examined SOX9 expression in CCA patients, including intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA), by immunohistochemistry. Association of SOX9 expression and clinical outcome was evaluated. A SOX9 gene signature and its biological functions were investigated in CCA cell lines. My results reveal that SOX9 expression is significantly associated with overall survival of iCCA patients, with high SOX9 expression presenting with a shorter survival time, as compared to patients with low SOX9. Impressively, in the investigated patient cohort, CCA patients with low SOX9 levels have 62 months of median survival time following chemotherapy, whereas median survival time is only 22 months for patients with high SOX9 expression. *In vitro*, gemcitabine treatment induces SOX9 expression in CCA cells. When SOX9 is knocked down by small interfering RNA (siRNA), gemcitabine-induced cell death is markedly increased. Molecularly, SOX9 silencing inhibits gemcitabine-induced phosphorylation of checkpoint kinase 1 (CHEK1), a key cell cycle check point regulator that coordinates the DNA damage response and expression of multidrug resistance genes. Microarray analyses show that SOX9 knockdown in CCA cells alters the gene signature with respect to adenosine triphosphate–binding cassette (ABC) transporters, drug metabolism enzymes and p53 signaling. Moreover, I demonstrate that SOX9 expression is required for survival, migration and stemness of CCA cells. Finally, I found out that EGFR/ERK1/2 signaling is important in regulating SOX9 expression in CCA cells.

In conclusion, my thesis has revealed that (1) SOX9 is critical for CCA cell survival, migration and CSCs-features, (2) governs the response of CCA cells to chemotherapy through regulating activation of CHEK1and multidrug resistance genes. (3) My data also provide a strong rational for a clinical study to confirm SOX9 as a biomarker to predict which CCA patients are eligible for efficient chemotherapy.