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

PRRX1 expression and functions in hepatocellular carcinoma

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Background & Aims: Hepatocellular carcinoma (HCC) is the most frequently diagnosed liver cancer and a leading cause of cancer-related death. Paired related homeobox 1 (PRRX1) is a transcriptional co-activator, which regulates cell growth, differentiation and, as I could recently show, is also linked to epithelial to mesenchymal transition (EMT). EMT is a hallmark of cancer progression, paving the way to tumor cell spreading into surrounding tissue, vessels and other organs. The transforming growth factor-β (TGF-β) is a known EMT inducer that also plays important roles in HCC. Whether *PRRX1* has a functional relevance in HCC is still unknown. Thus, the aim of my work was to perform an in-depth analysis of *PRRX1* expression and its co-expressed genes in HCC samples, as well as to clarify its function in liver carcinogenesis.
Methods: The expression of *PRRX1* in human HCC was assessed in online databases, including Oncomine, cBioPortal, and in microarray datasets encompassing > 1,400 liver tumor profiles. Bioinformatics analyses were performed for functional annotation of genes correlated with *PRRX1* in HCC, and followed by Kaplan-Meier overall survival analyses. *In vitro*, *PRRX1* expression was analyzed in HCC cell lines, treated or not with TGF-β, its receptor inhibitor Galunisertib. Further, *PRRX1* expression was inhibited with small interfering RNA and the functional impact on cell migration, proliferation, clonogenicity, apoptosis and metabolism were measured.
Result: *PRRX1* is frequently upregulated in human HCC. Patients with high *PRRX1* show elevated expression of *TGFBR1*. The genes positively correlated with *PRRX1* display enrichment in crucial features of cancer, including stroma remodeling, signal transduction, downregulated metabolic pathways, focal adhesion and EMT. I could identify two EMT-related transcription factors, *ZEB1* and *ZEB2,* as novel *PRRX1*-related genes in HCC. *PRRX1* in combination with *ZEB*s significantly predicted survival outcome in HCC patient cohorts investigated. In HCC cell lines, TGF-β1 treatment increases expression of *PRRX1*. *PRRX1* influences cell migration and modulates expression of EMT markers in a cell type dependent-manner. *PRRX1* knockdown increases cell proliferation and clonogenicity. Further, knock down of *PRRX1* promotes glucose consumption (Warburg effect), regulates core metabolic genes and levels of TCA cycle metabolites and amino acids. Moreover, depleting *PRRX1* causes upregulation of genes regulating fatty acid biosynthesis and oxidation with influence on fatty acid levels.
Conclusion: The findings of my study provide evidence for a functional role of *PRRX1* in HCC, including a master control on pathways that facilitate tumor progression, including modulation of cell metabolism. The new findings on *PRRX1* functions suggest further in-depth mechanistic studies on the relevance of *PRRX1* in human liver cancer.