YB-1 transcription factor promotes Sorafenib resistance in Liver Cancer

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Background: Hepatocellular carcinoma (HCC) is a primary malignant liver tumor that commonly occurs as a progression of chronic liver inflammation. Sorafenib is the standard first-line systemic drug for advanced HCC, but the acquired resistance to sorafenib results in limited benefits. The mechanism underlying sorafenib resistance in HCC remains unclear. Recently, we have identified a multifunctional oncoprotein Y-box binding protein-1 (YB-1) that dysregulates a wide range of genes involved in drug resistance in other cancers and is responsible for increasing the IC-50 of sorafenib in HCC cell lines. In this study we will analyze the signaling pathways and genes regulated by YB-1, that is responsible for increasing sorafenib resistant in liver cancer cells.

Methods: HCC cell lines SK-Hep-1, C3A, HepG2 and Hep-3B were treated with Sorafenib and the IC-50 was calculated using MTT assay. RNA and protein of YB-1 was analyzed using RT-PCR and western blot respectively. Lentiviral based overexpression and knockdown of YB1 was performed in these cell lines and sorafenib IC50 were calculated to verify its role in Sorafenib resistance. Development of sorafenib resistant cell line is in progress.

Results: IC-50 values calculated from MTT assays of the HCC cell lines were compared with the YB-1 protein expression in four liver cancer cell lines. Knockdown of YB-1 re-sensitized cell lines to Sorafenib. We have developed Sorafenib resistant cell lines to further study the mechanism of YB-1 mediated drug resistance.

Conclusion: This study will establish oncogenic YB-1 protein as an effective therapeutic target to overcome sorafenib resistance in liver cancer.