# The Gene Expression Level of Transforming Growth Factor-beta (TGF-beta) and Significance of Survivin in Hepatocellular Carcinoma

**Submitted by**

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بسم الله الرحمن الرحيم

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا

إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ

الْحَكِيمُ﴾

صدق الله العظيم

البقرة – الآية 32

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*I declare that this thesis has been composed by myself and the work herein has not been submitted for a degree at this or any other university.*

*Ahmed Fathi Soliman*

*I dedicate this work to my mother's soul, my father and my family. I have to thank them for supporting me with kindness and patience.*

*Ahmed Fathi Soliman*

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***Ahmed F. Soliman***

**The Gene Expression Level of Transforming Growth Factor-beta (TGF-beta) and Significance of Survivin in Hepatocellular Carcinoma**

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# *Abstract*

**Background and objective:** Transforming growth factor-β1 (TGF-β1) plays an important role in the regulation of cell growth and differentiation, angiogenesis, extracellular matrix formation, immunosuppression and cancer development. Survivin was shown to inhibit apoptosis and accelerate cancer cell proliferation as well. In this study, investigation included the levels of circulating TGF-β1 and hepatic TGF-β1 mRNA expression, and their diagnostic value for hepatocellular carcinoma (HCC). Also expression of survivin protein was investigated which may be of a diagnostic significance and therapeutic relevance in HCC.

**Patients and methods:** A total of 50 individuals were enrolled, which included 24 patients with primary HCC, 21 with chronic hepatitis C virus (HCV) infection, as well as 5 healthy subjects.

TGF-β1 gene expression level of tumors and of non-cancerous livers was analyzed by real-time reverse transcriptase polymerase chain reaction (RT-PCR), while serum TGF-β1 and AFP were assessed by enzyme linked immune-sorbent assay (ELISA). Also the expression of survivin protein was detected by immunohistochemistry and the percentage of apoptotic cells (apoptotic index; AI) was evaluated with TUNEL assay.

**Results:** The patients with HCC had significantly higher hepatic TGF-β1 gene expression levels (87.55 ± 15.22; mean ± SE) than HCV patients (22.7 ± 4.21) ($p<0.001$), also serum TGF-β1 was significantly increased in

HCC patients (16.93 ± 0.90 ng/ml) as compared to HCV patients (13.67 ± 0.81 ng/ml) ($p<0.05$). Survivin expression and TUNEL labeling index (LI) for apoptotic cells were significantly higher in HCC than in HCV livers ($p<0.05$ and $p<0.001$, respectively).

The sensitivity, specificity, positive and negative predictive values of hepatic TGF-β1 gene expression was 91.7, 76.2, 81.5, and 88.9%, respectively, while the values for serum TGF-β1 were 75, 61.9, 69.23, and 68.42%, respectively. Combining hepatic TGF-β1 gene expression and either serum TGF-β1 or serum AFP raised the sensitivity to 95.8%. Also, combining serum TGF-β1 and serum AFP raised the specificity to 95.2%.

In HCV patients, a positive correlation between serum AFP level and hepatic survivin protein expression was recorded. Also, hepatic TGF-β1 gene expression level was correlated positively with serum TGF-β1 level. In HCC patients, survivin protein expression was correlated negatively with TUNEL LI. On the other hand, serum AFP level was correlated positively with HCC grade and stage.

**Conclusion:** The over-expression of TGF-β1 gene and its downstream protein level could lead to enhanced tumor cell proliferation. Also TGF-β1 serum concentration may help early diagnosis of HCC. Concerning survivin, it may be a useful diagnostic marker of cancer and a potential target for cancer treatment.

# *Contents*

# *List of Tables*

# *List of Tables (Cont.)*

# *List of Figures*