Nahed Baddour et al., Surgery Curr Res 2018, Volume 8
DOI: 10.4172/2161-1076-C1-036

Identification of the possible therapeutic targets in the insulin-like growth factor 1R pathway in a cohort of Egyptian hepatocellular carcinoma complicating chronic hepatitis c type 4

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Background: Hepatocellular carcinoma (HCC) presents with widely varying biological behavioral patterns. This may stem from its diverse etiologies including different types of viruses, non-viral etiologies and environmental factors. This widely diverse natural history may reflect the underlying molecular mechanisms involved in the process of hepatic carcinogenesis in Egyptian patients complicating hepatitis C virus (HCV) type 4.

Aim: Determination of the gene expression pattern of a cohort of biopsies from cases of Egyptian HCCs complicating chronic HCV genotype 4 using qRT-PCR technology using Human Insulin Signaling Pathway RT2 Profiler PCR Array which includes primers for 84 insulin pathway related genes.

Methods: Total RNA was extracted from 32 formalin fixed paraffin embedded tissues of human hepatocellular carcinoma cases and six healthy liver donors to be used as normal controls, followed by reverse transcription of the RNA to cDNA. We then performed qRT-PCR using Human Insulin Signaling Pathway RT2 Profiler PCR Array (QIAGEN) to determine the expression levels of 84 insulin signaling pathway related genes. The gene expression levels were correlated to different patient/tumor characteristics.

Results: Gene dysregulation was observed in HCC patients relative to control group. Six genes namely AEBP1, AKT2, FOS, PIK3R1, PRKCI, SHC1 were significantly overexpressed in HCC patients relative to the control group. SHC1 was the most significantly overexpressed gene (0.001). On the other hand, 13 genes, namely ADRB3, DUSP14, ERCC1, FRS3, IGF2, INS, IRS1, JUN, MTOR, tPIK3R2, PPP1CA, RPS6KA1 and VEGF were significantly under expressed in HCC patients relative to the control group, where PPP1CA and INS were the two most significantly under expressed genes (0.002). Statistically significant differences in the levels of expression of GSK3A (0.002) were observed between low and high grade HCCs. Also, significant differences were seen in the expression of AEBP1 (0.040), AKT1 (0.024) and FBP1 (0.007) between patients below and above 60 years of age. DOK1 (0.037) was expressed at significantly higher levels in females as compared to male patients. RPS6KA1 (0.034) was significantly under expressed in HBcAg positive cases as compared to negative ones. AKT1 (0.019) and MAPK1 (0.017) were significantly upregulated in the presence of aflatoxin positivity, whereas RPS6KA1 (0.046) was significantly under expressed. In cases with thrombocytopenia, AKT1 (0.038) was significantly upregulated, BCL2L1 (0.045) was significantly downregulated as was VEGFA (0.038). Cases with high AFP levels showed significant upregulation of AKT2 .021) and PRKCI (0.016).

Conclusion: Therapy of HCC has to be based on the molecular characteristics of the particular tumor at hand. The gene expression patterns identified in this study, especially the upregulated ones may serve as possible targets for therapy of HCC patients.

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