

8- Role of TGF- β 1 and C-Kit Mutations in Hepatocellular Carcinoma Progression in Patients with Hepatitis C Virus: in vitro study

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Abstract:

Transforming growth factor- β (TGF- β) is considered a tumor suppressor cytokine in normal and non-malignant conditions. Yet, in malignancy, TGF- β can exert opposite effects that cancer cells may exploit for their usefulness. C-Kit plays a prominent role in stem cell activation and liver regeneration after injury. However, little is known about cross-talk between TGF- β and C-Kit and its role in hepatocellular carcinoma (HCC) progression. Here, we studied the effect of increasing doses of TGF- β 1 on CD44⁺CD90⁺ liver stem cells (LSCs) and C-Kit gene expression of malignant and adjacent non-malignant liver tissues excised from 32 HCC patients. Results showed that malignant LSCs percentage was 2.0-fold higher compared to their non-malignant counterparts. When treated with increasing doses of TGF- β 1, malignant and non-malignant LSCs were progressively suppressed, but low TGF- β 1 dose failed to suppress their malignant counterparts. Moreover, in contrast to malignant liver cells, C-Kit exon 9 and 11 were not expressed in their non-malignant counterparts. Mutation analysis of C-Kit detected mutations in exon 9, but not in exon 11, in some malignant liver cells resulting in the change of amino acid sequence and deregulated protein structure and function. Interestingly, in malignant liver cells, mutated exon 9 were shown to be associated with high viremia hepatitis C virus (HCV) and their expression was not suppressed on TGF- β 1 treatment at all doses. To our knowledge, this is the first report that the C-Kit gene is mutated in high viremia HCV-associated HCC patients. Our study underscores the need to investigate TGF- β 1 level and C-Kit mutations in patients with chronic HCV for HCC prevention and better therapeutic management.

Key Words: HCC, chronic liver disease, TGF- β 1, liver stem cells, C-Kit mutations.

Abbreviations: HCC, Hepatocellular carcinoma; TGF- β 1, Transforming growth factor beta one; LSC, Liver stem cell; CSC, Cancer stem cell; SCF, Stem cell factor; C-Kit, Stem cell factor receptor; HCV, Hepatitis C virus