Disruption of growth inhibitory Transforming growth factor-β1 signaling pathways in human hepatocellular carcinoma cancer cells

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Background Transforming growth factor-β1 (TGF-β1) causes growth inhibition in many cell types. Its role in the outgrowth of human hepatocellular carcinoma (HCC) is still unknown.

Methods We investigated the growth inhibitory effects of TGF-β1 by DNA synthesis assay, genetic integrity of TGF-β receptors, transcriprional responses to TGF-β1 by Southern and Northern analysis, and the expression level of cell cycle regulating proteins by Western analysis in 11 human HCC cell lines.

Results Three (27%) out of 11 cell lines showed growth inhibition to TGF-β1. We performed Southern and Northern analysis of TGF-β type I and II receptors (TRI and TRII, respectively) and examined poly-adenine track mutation of TRII, but failed to find any genetic mutation, implying that the receptor complex might be active. The transcriprional induction of PAI-1 and p21WAF1/CIP1 were detected in all HCC cell lines. Homozygous deletions of the p15INK4b gene were found in 2 cell lines, and p15INK4b was upregulated in 7 out of 9 cell lines in response to TGF-β1. Amplification and overexpression of the cyclin D1 gene was detected in 4 (50%) out of 8 HCC cells that showed the growth inhibition to TGF-β1. In addition, transfection studies were performed to determine whether the suppression of cyclin D1 expression with antisense cyclin D1 could recover the sensitivity to TGF-β1 in growth inhibition in a TGF-β1 resistant HCC cell line containing amplified cyclin D1 gene.

Conclusion The disruption of distal components in the TGF-β1 signaling pathway as well as amplification and overexpression of cyclin D1 are responsible for the resistance to growth inhibitory effects of TGF-β1 in eight out of 11 human HCC cell lines.