UPREGULATION OF A NOVEL PROTEIN IN HCC ENHANCES CANCER CELL SURVIVAL BY SUPPRESSING SPECIFIC APOPTOTIC EFFECTORS.

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Background and Aims: Altered cell survival is a hallmark of cancer, including primary HCC. The aim of our study is to identify novel anti-apoptotic genes promoting liver tumourigenesis.

Methods: We used a combination of *in vitro* and *in vivo* analyses to identify novel anti-apoptotic genes. We compared the ability of HCC cells stable-expressing either shRNA against HD (a newly-identified anti-apoptotic molecule) or control shRNA to growth in vivo and in vitro.

Results: By examining the expression pattern of HD mRNA in a panel of human neoplasms and cancer cells, we demonstrated that HD is highly expressed in both HCC cells and liver biopsies. mRNA profiling showed significantly higher expression of HD transcripts in HCC samples compared to normal livers (**P=0.0062) and adjacent non-tumor tissues (***P<0.0001). Elevated HD expression also correlates with HCC progression and poor prognosis. Protein analyses confirmed that HD levels were significantly increased in HCC tissues and hepatoma lines compared to healthy livers. Notably, xenograft experiments demonstrated that suppression of HD strongly impaired tumor formation in vivo. Knockdown of HD significantly reduced proliferation and markedly increased apoptosis of hepatoma cells.

Conclusion: We report that HD mRNA and protein are frequently overexpressed in HCC tissue compared with non-tumour liver tissues, where it correlates with poor patient survival. Enforced expression of HD was sufficient to enhance cell survival, whereas silencing of HD was greatly enhances apoptosis. Notably, HD attenuation in HCC cells also suppressed activation of specific apoptotic markers, thus suggesting that HD is an important novel anti-apoptotic marker for liver tumourigenesis.