



# HBx sensitizes HCC cell lines to lapatinib by up-regulating ErbB3

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## Abstract

### Background & Aims

Poor prognosis of hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) involves HBV X protein (HBx)-induced tumor progression. HBx also contributes to chemoresistance via inducing the expressions of anti-apoptosis and multiple drug resistance (MDR) genes. Targeting multiple receptor tyrosine kinases (RTKs) by sorafenib showed clinical benefits in HCC patients. However, the impact of HBx expression on the therapeutic efficacy of RTK inhibitors remains unknown.

### Methods

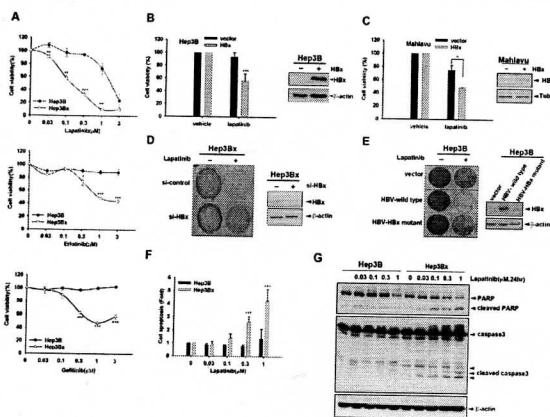
The viabilities of HCC cells and their HBx-overexpressing derivatives in response to RTK inhibitors were analyzed by using MTT, cell counting, and colonogenic assay. The mRNA and protein expression of gene expressions were examined by reverse-transcription quantitative polymerase chain reaction (RT-qPCR) and Western blot analysis. The gene promoter activity was determined by luciferase assay.

### Results

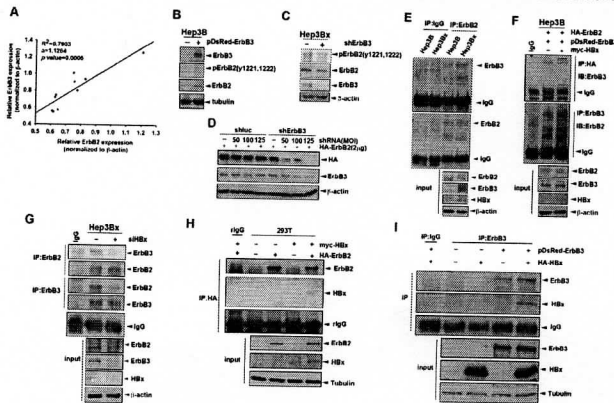
HBx overexpression did not alter the cellular sensitivity of HCC cell lines to sorafenib, but unexpectedly enhanced the cell death induced by EGFR family inhibitors, including gefitinib, erlotinib, and lapatinib. Mechanistically, HBx transcriptionally upregulates ErbB3 expression in a NF- $\kappa$ B-dependent manner. In addition, HBx also interacts with HER2 and ErbB3 proteins and enhances the formation of HER2/ErbB3 heterodimeric complex. The cell viability of HBx-overexpressing cells was decreased by silencing ErbB3 expression, further revealing the pivotal role of ErbB3 in HBx-mediated cell survival.

## Result

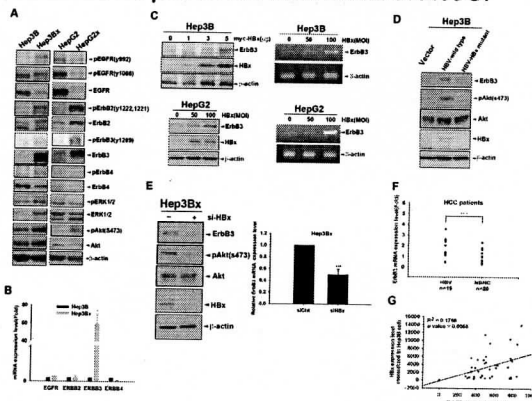
### Overexpression of HBx increases the sensitivity of HCC cell lines to EGFR/HER2 TKIs.



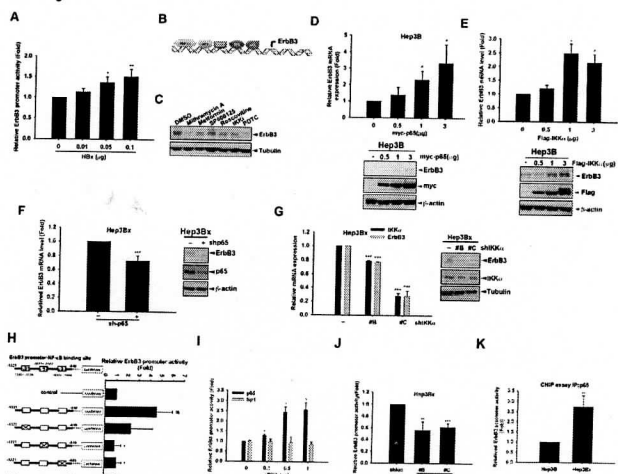
### Overexpression of HBx enhanced the dimerization of ErbB2 and ErbB3.



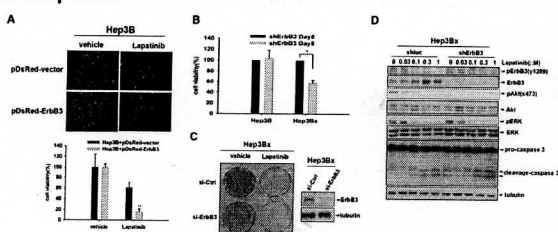
### HBx increases the protein and mRNA levels of ErbB3.



### HBx induced ErbB3 expression through enhancing ErbB3 promoter activity.



### ErbB3 overexpression enhances the sensitization of HCC cell lines to lapatinib.



## Conclusion

