Suppression of Maspin by IKKα-dependent MicroRNAs Confer HBx-mediated Hepatocellular Cancer Progression

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Abstract

Background & Aims

Hepatocellular carcinoma (HCC) is a heterogeneous disease implicated by diverse risk factors including viral infections. Mammary serine protease inhibitor (Maspin) is a well-known tumor suppressor in some types of solid tumors, but its role in HCC is poorly understood. This study aimed to explore gene regulation of maspin and its relationship with HCC patient prognosis.

Methods

We examined the correlation between maspin expression and HCC prognosis by analyzing RNA and protein expressions in human HCC samples with real-time polymerase chain reaction, immunohistochemical, and immunoblot analyses. The roles of maspin and hepatitis B virus (HBV) X protein (HBx) in chemosensitivity, anoikis resistance, and motility of HCC cells were examined in MTT and migration assays. Maspin-targeting microRNAs were identified in microarray, bioinformatic, luciferase reporter, and RNA-immunoprecipitation analyses.

Results

Our data revealed that maspin expression was specifically reduced in HBV-associated HCC patients and correlated with their poor prognosis. The downregulation of maspin was induced by HBx overexpression to promote motility, anoikis resistance, and chemoresistance of HCC cells. Transcriptional induction of microRNA-7, -103, -107, and -21 by HBx in a nuclear IKKα/NFκB-dependent manner was further demonstrated to directly target maspin mRNA, leading to its protein downregulation. Higher expressions of nuclear IKKα and these microRNAs also correlated with maspin downregulation, and associated with the poor overall survival of HBV-associated HCC patients.

Conclusions

These data not only provided new insights into the molecular mechanisms of maspin deficiency by HBx, but also indicated that downregulation of maspin by microRNAs may confer HBx-mediated metastasis and chemoresistance in HCC.

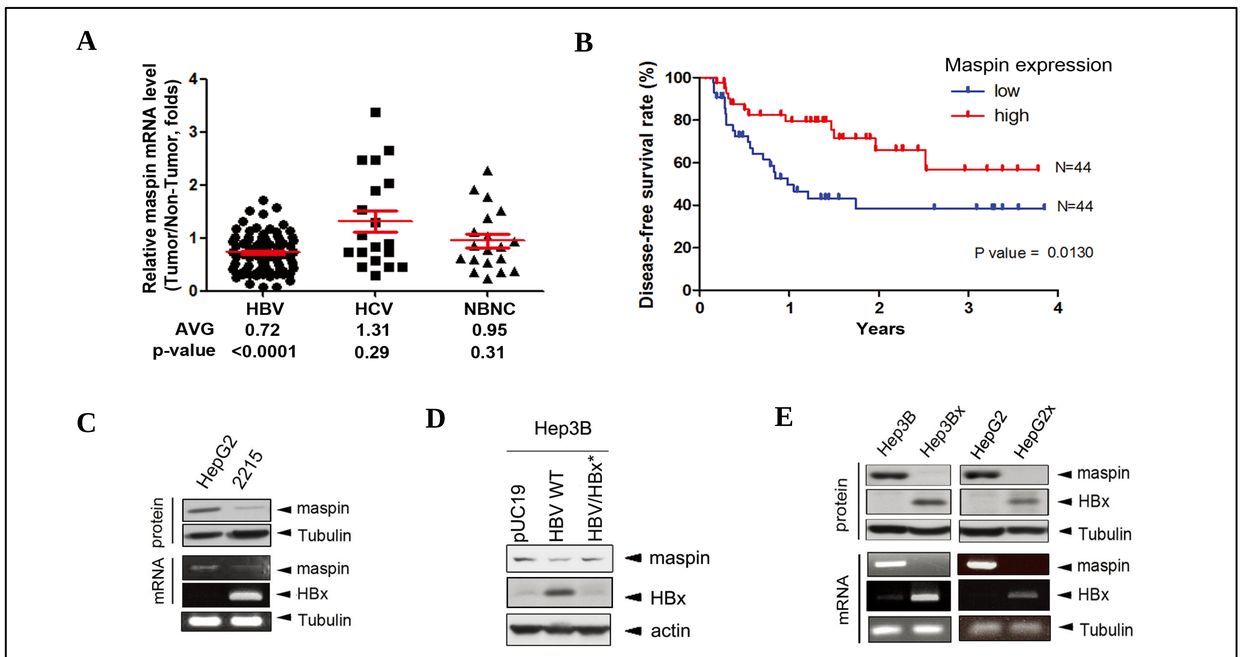

Figure 1. HBx-mediated maspin suppression correlated with poor prognosis of HCC patients.

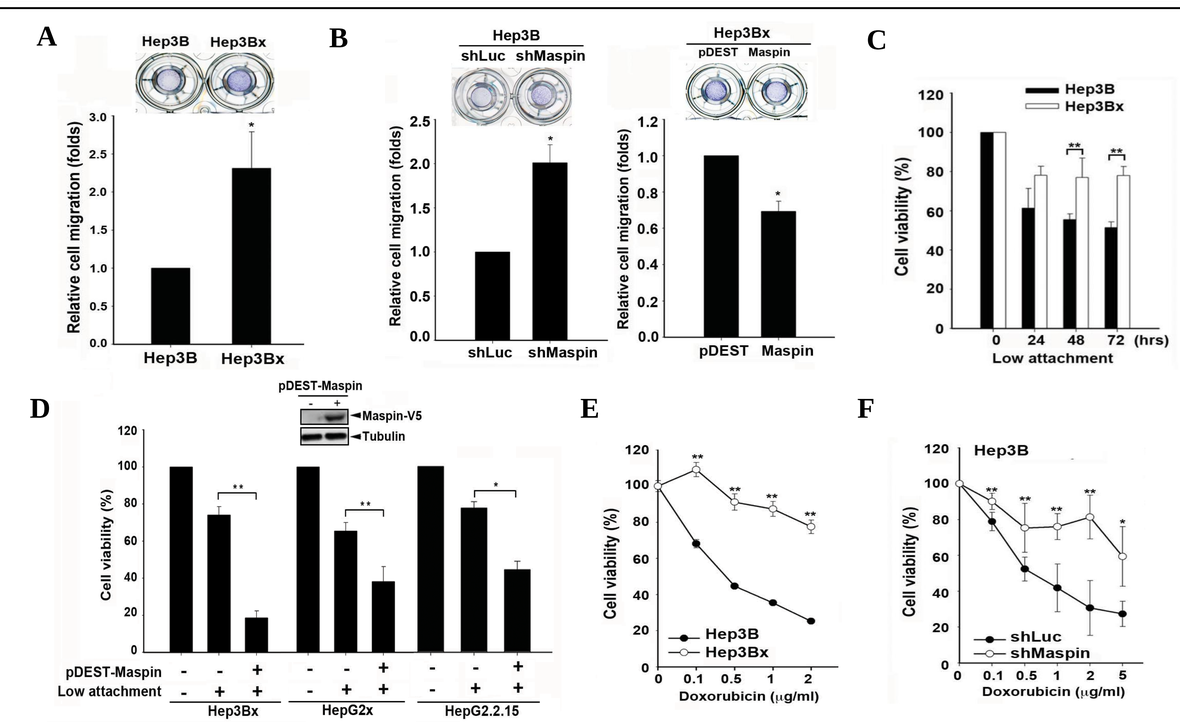

Figure 2. Maspin suppression confers to HBx-induced migration, anoikis resistance, and chemoresistance in HCC cells.

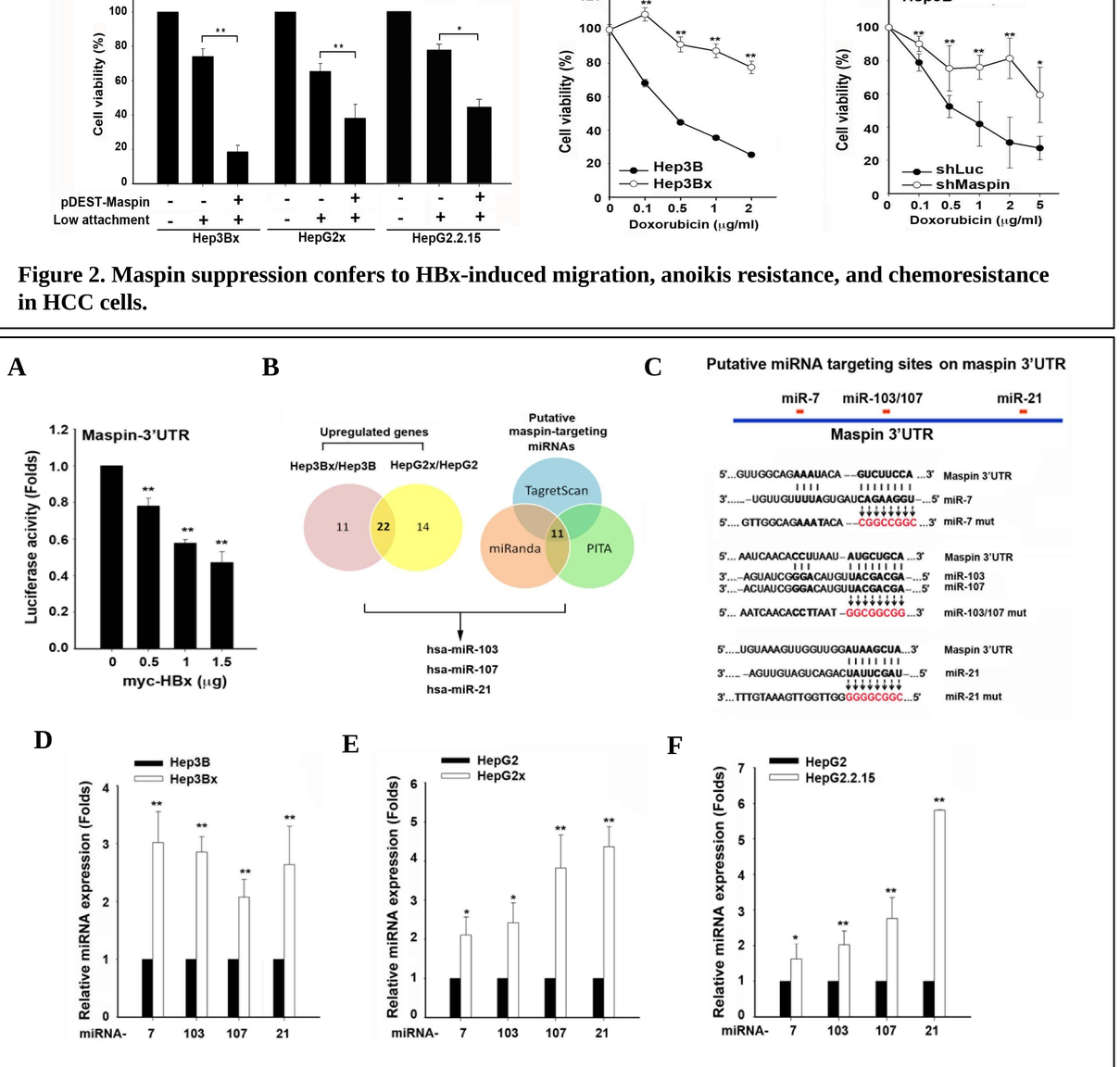

Figure 3. Overexpression of HBx induced microRNAs-7, -21, -103, and -107 to suppress maspin expression.

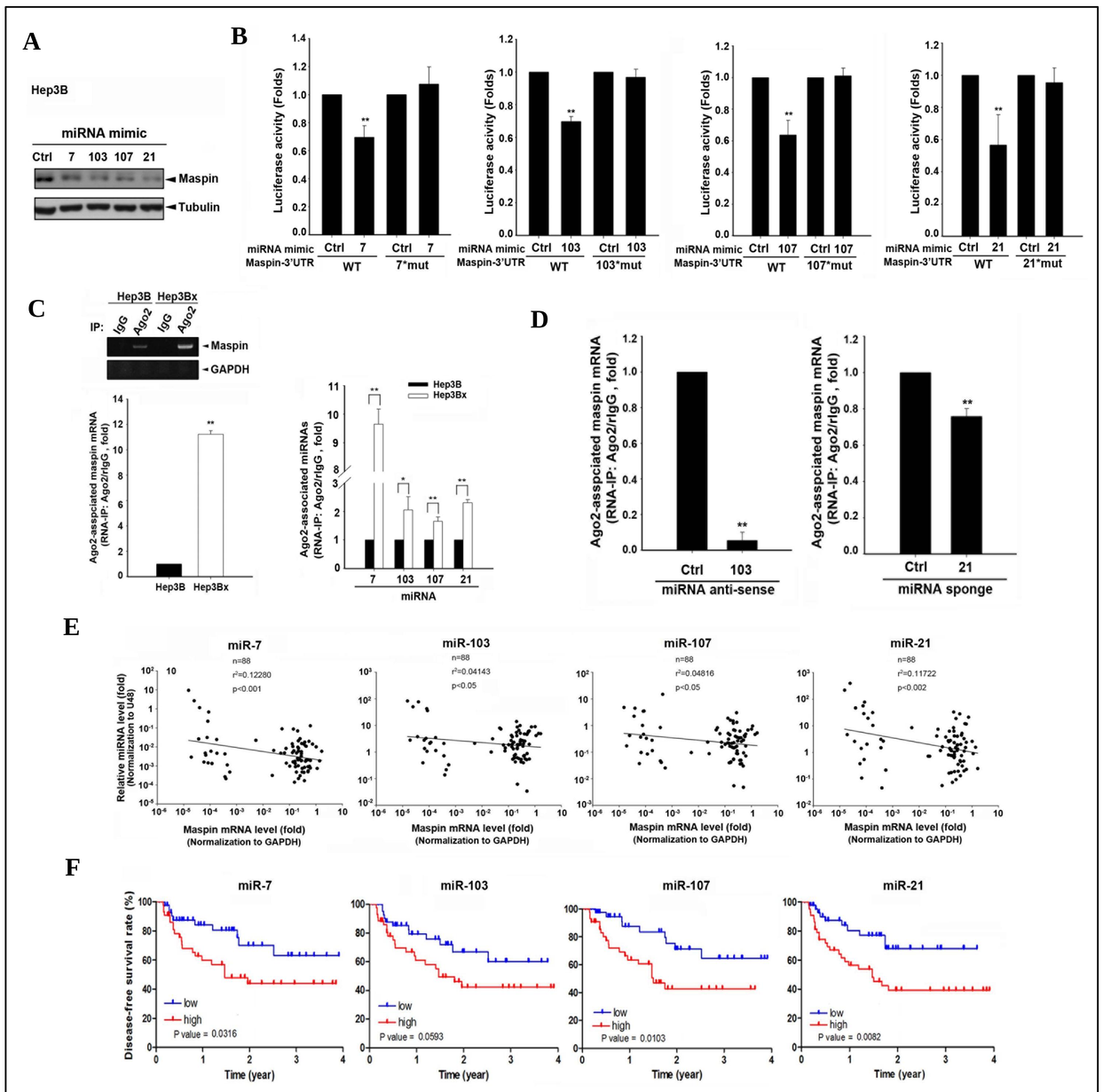

Figure 4. Induction of maspin-targeting microRNAs by HBx correlated with the poor prognosis of HBV-associated HCC patients.

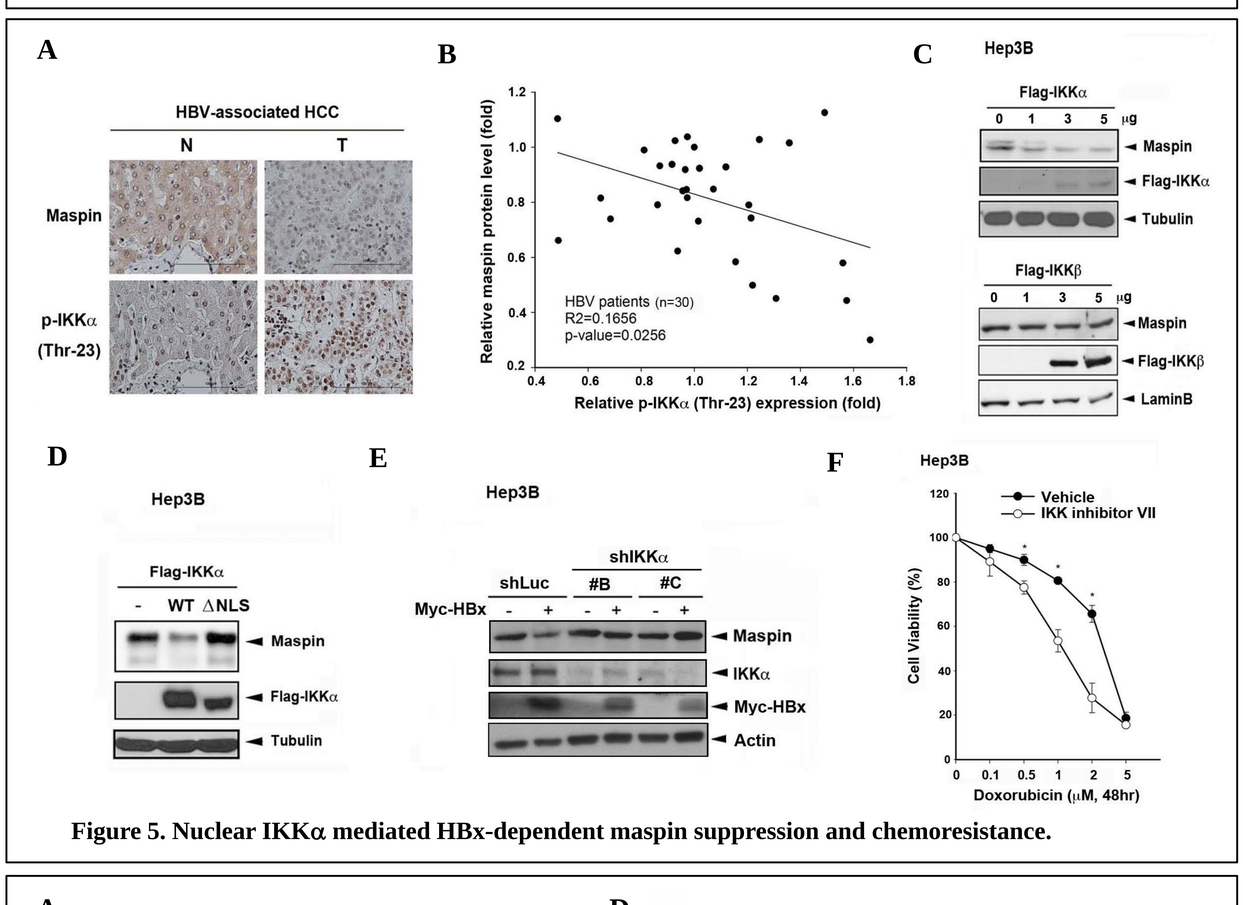

Figure 5. Nuclear IKKα mediated HBx-dependent maspin suppression and chemoresistance.

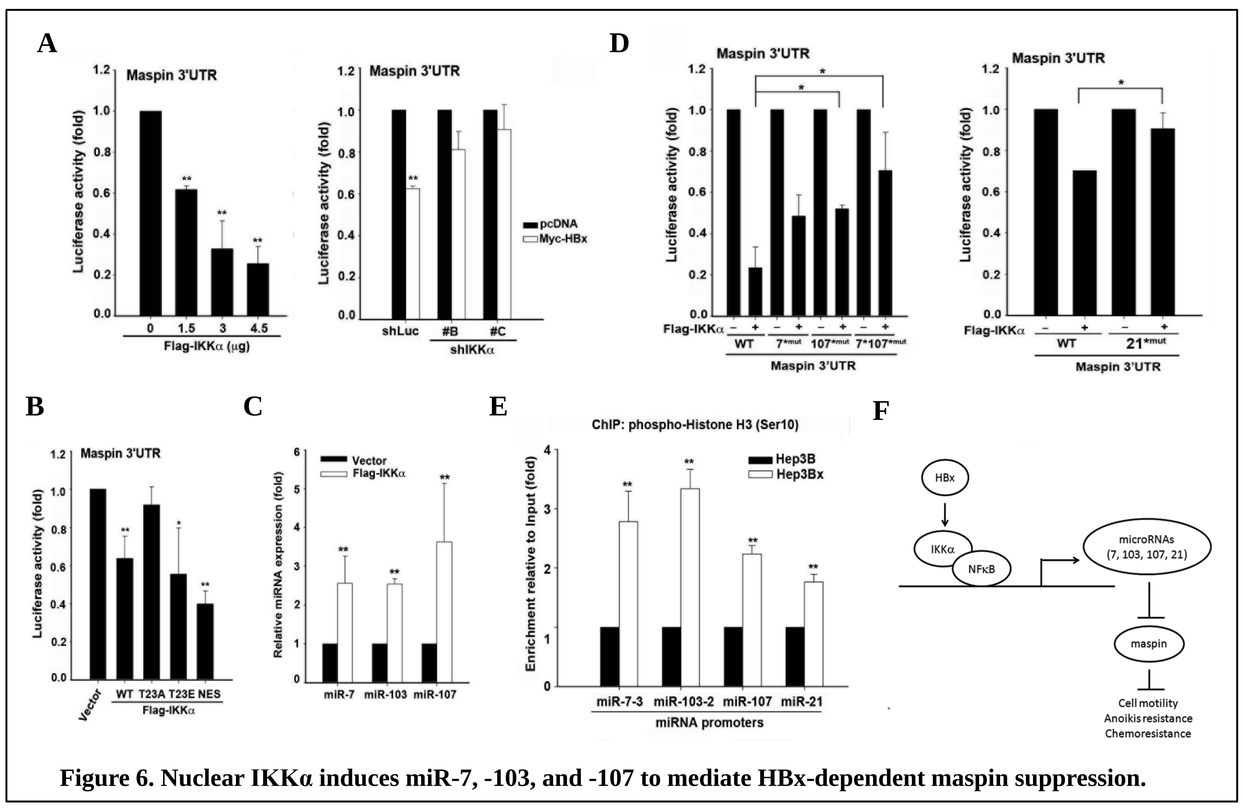

Figure 6. Nuclear IKKα induces miR-7, -103, and -107 to mediate HBx-dependent maspin suppression.

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