Suppression of maspin by IKKα-dependent microRNAs contributes to HBx-mediated human hepatocellular carcinoma progression

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Abstract

Maspin suppresses tumor progression by promoting cell adhesion and apoptosis and by inhibiting cell motility. Maspin deficiency was observed in some cancer types. However, its role in tumorigenesis of hepatocellular carcinoma (HCC) remains unclear. The gene regulation of maspin and its relationship with HCC patient prognosis were investigated in this study. Our data revealed that maspin expression was specifically reduced in HBV-associated patients and correlated with their poor prognosis. Maspin downregulation in HCC cells was induced by HBx to promote their motility and resistance to anoikis and chemotherapy. Transcriptional induction of microRNA-7, -103, -107, and -21 by HBx in a nuclear IKKα-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 in HBV-associated patients, and were associated with their poor overall survival. 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 confers HBx-mediated aggressiveness and chemoresistance in HCC.

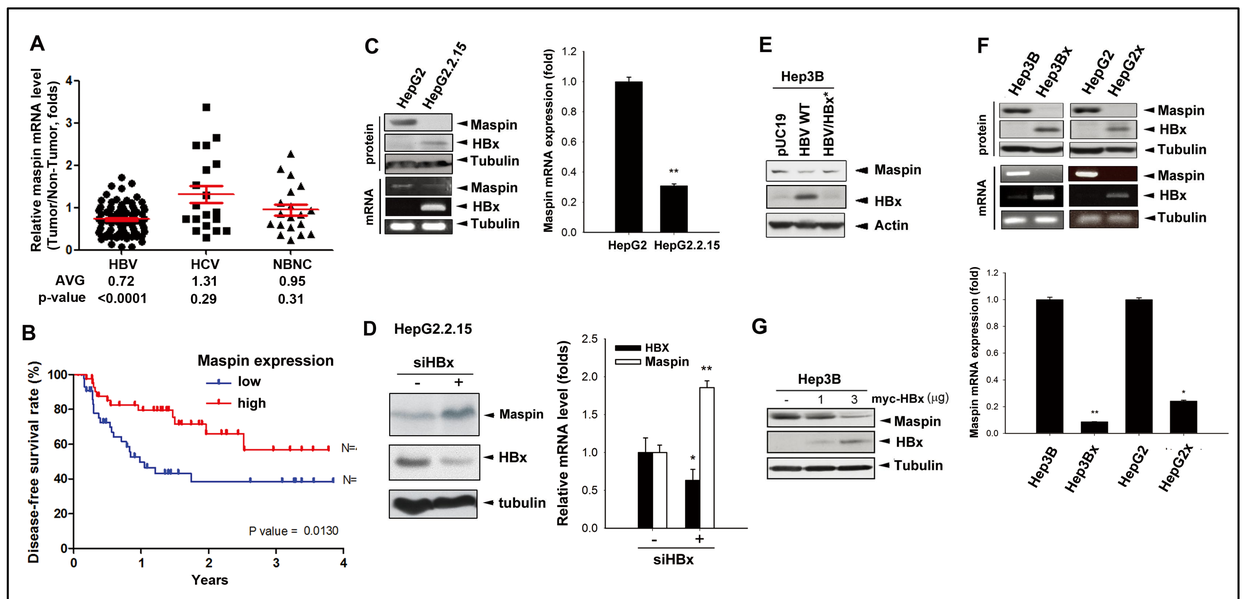

Figure 1. HBx-mediated maspin suppression correlated with poor prognosis of HBV-associated HCC patients.

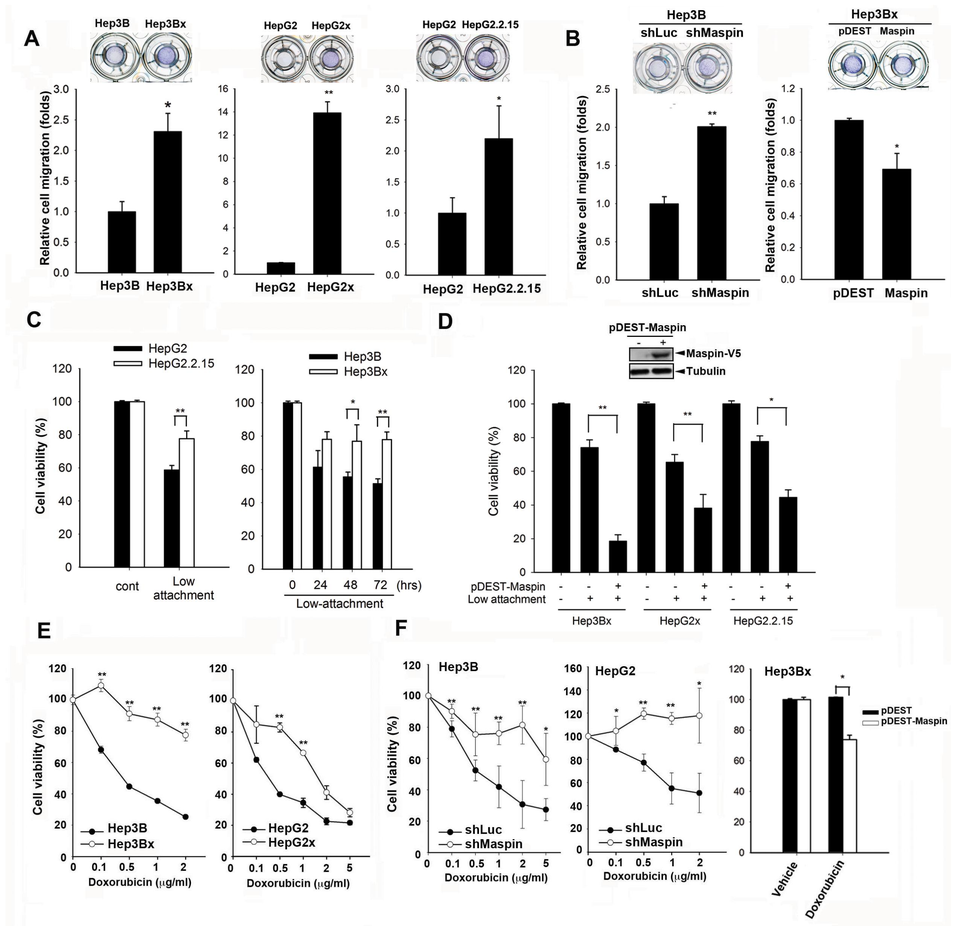

Figure 2. Maspin suppression confers to HBx-induced migration, anoikis resistance, and chemoresistance in HCC cells.

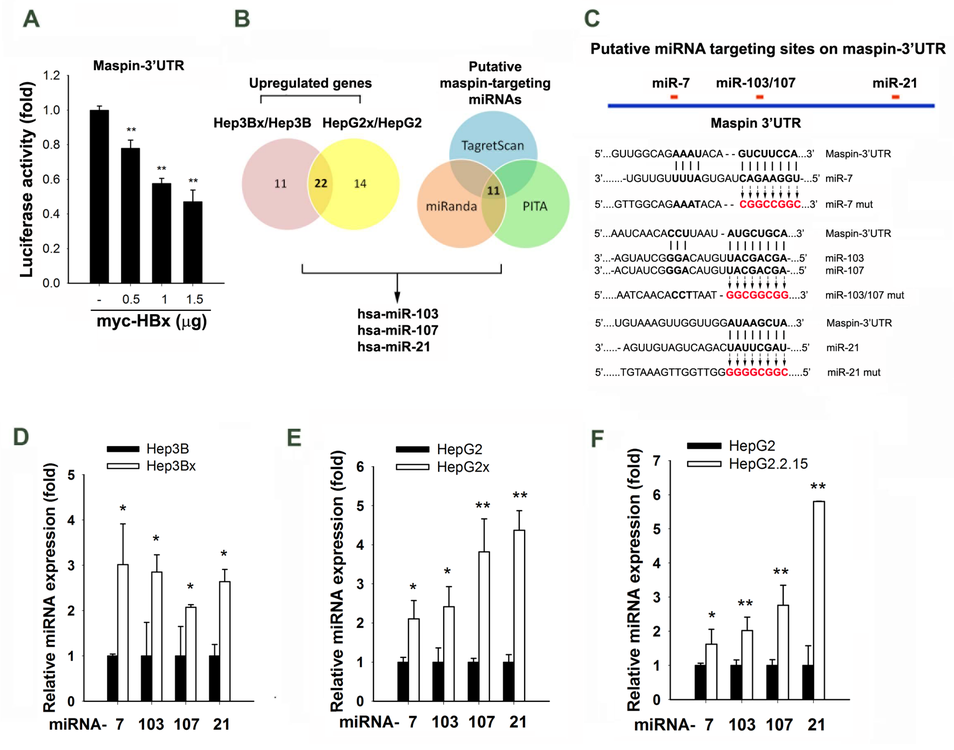

Figure 3. Overexpression of HBx induced microRNAs-7, -21, -103, and -107 to suppress maspin expression.

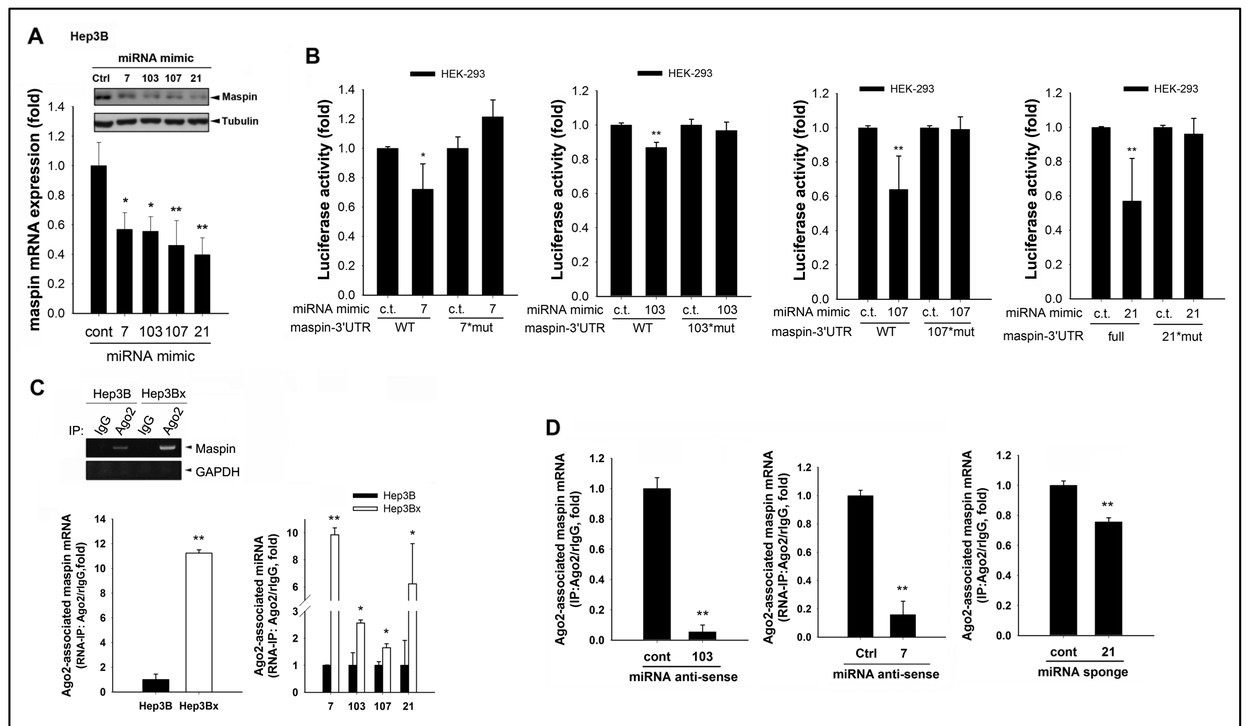

Figure 4. HBx-induced miRNAs suppressed maspin expression through directly interacting maspin 3'UTR.

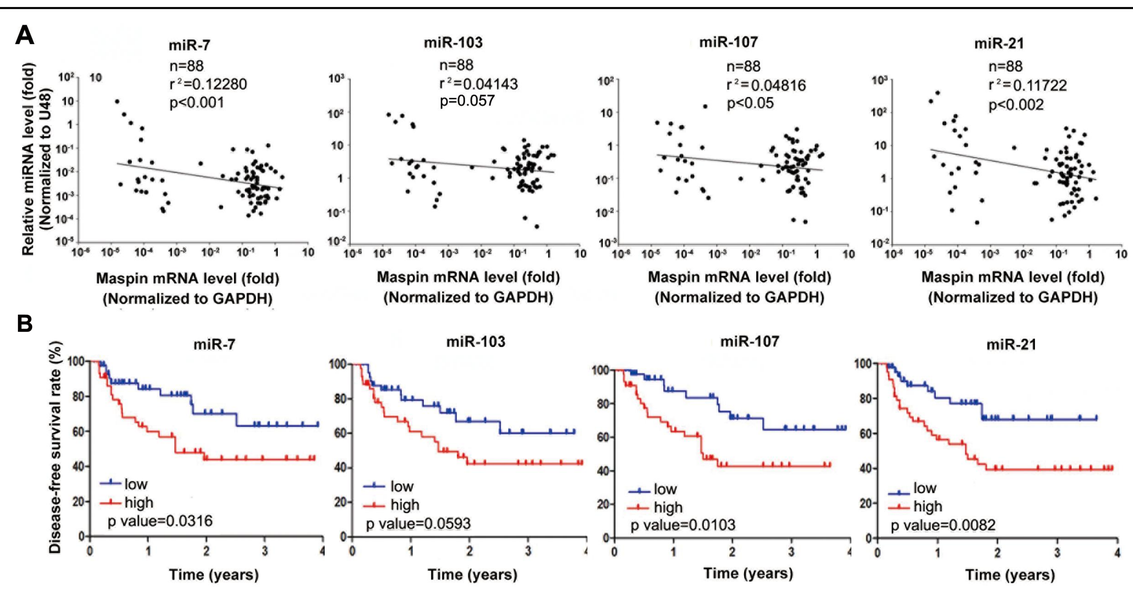

Figure 5. Induction of maspin-targeted microRNAs by HBx correlated with the poor prognosis of HBV-associated HCC patients.

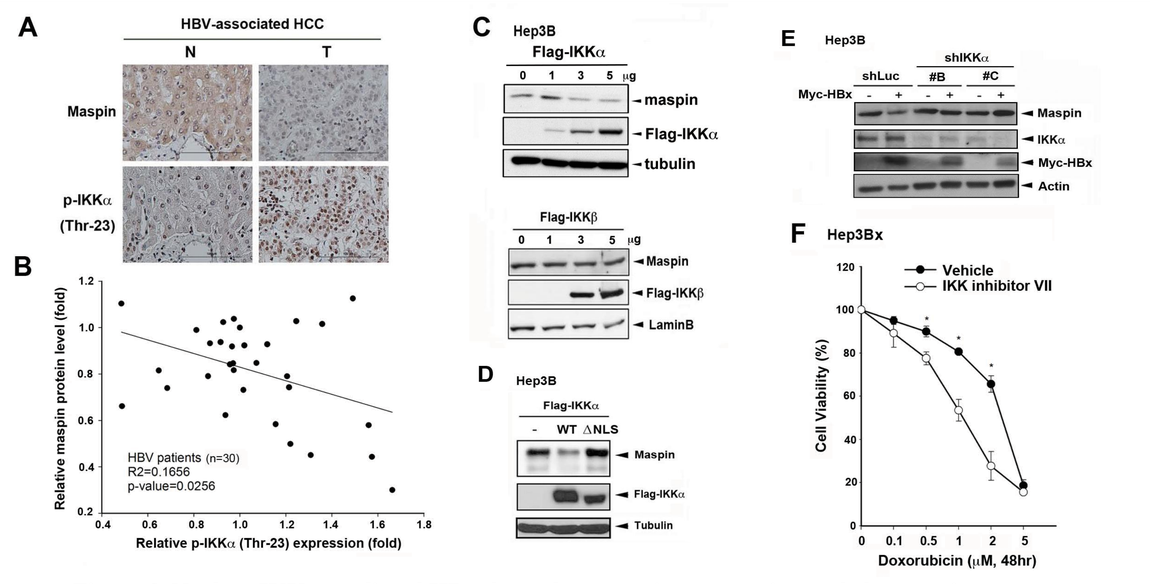

Figure 6. Nuclear IKKα mediated HBx-dependent maspin suppression and chemoresistance.

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

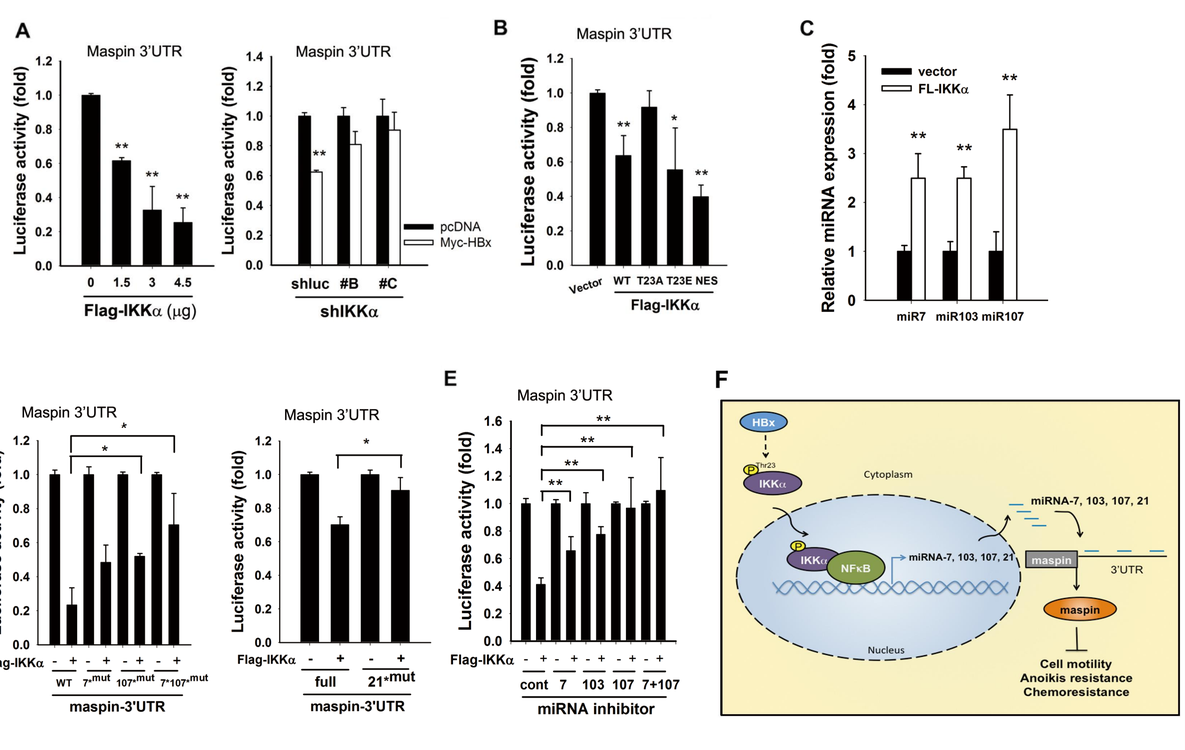

Figure 7. Nuclear IKKα induces miR-7, -103, and -107 to mediate HBx-dependent maspin suppression.