Hepatoma-derived growth factor/nucleolin axis as a novel oncogenic pathway in liver carcinogenesis

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ABSTRACT

Hepatoma-derived growth factor (HDGF) overexpression is involved in liver fibrosis and carcinogenesis. However, the receptor(s) and signaling for HDGF remain unclear. By using affinity chromatography and proteomic techniques, nucleolin (NCL) was identified and validated as a HDGF-interacting membrane protein in hepatoma cells. Exogenous HDGF elicited the membrane NCL accumulation within 0.5 hour by protein stabilization and transcriptional NCL upregulation within 24 hours. Blockade of surface NCL by antibodies neutralization potently suppressed HDGF uptake and HDGF-stimulated phosphatidylinositol 3-kinase (PI3K)/Akt signaling in hepatoma cells. By using rescectd hepatocellular carcinoma (HCC) tissues, immunohistochemical analysis revealed NCL overexpression was correlated with tumour grades, vascular invasion, serum alpha-fetoprotein levels and the poor survival in HCC patients. Multivariate analysis showed NCL was an independent prognostic factor for survival outcome of HCC patients after surgery. To delineate the role of NCL in liver carcinogenesis, ectopic NCL overexpression promoted the oncogenic behaviours and induced PI3K/Akt activation in hepatoma cells. Conversely, NCL knockdown by RNA interference attenuated the oncogenic behaviours and PI3K/Akt signaling, which could be partially rescued by exogenous HDGF supply. In summary, this study provides the first evidence that surface NCL transmits the oncogenic signaling of HDGF and facilitates a novel diagnostic and therapeutic target for HCC.