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Cellular mechanisms of hepatocyte growth factor-mediated urokinase plasminogen activator secretion by MAPK signaling in hepatocellular carcinoma

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ABSTRACT

Aims and background. The hepatocyte growth factor, its receptor c-Met, and urokinase-type plasminogen mediate various cellular responses on activation, including proliferation, survival, invasion, and metastasis. The regulatory mechanisms for the proliferation and the particular invasive phenotypes of hepatocellular carcinoma are not yet fully understood. In order to clarify the intracellular downstream signal for hepatocyte growth factor/c-Met signaling in tumor progression and metastasis in hepatoma, we determined the effects of a specific MEK1 inhibitor (PD 098059) and a p38 kinase inhibitor (SB 203580) on hepatocyte growth factor-mediated cell proliferation and urokinase-type plasminogen expression in hepatoma cell lines (HepG2 and Hep3B).

Results. Hepatocyte growth factor treatment induced the phosphorylation of ERK and p38 kinase in a dose-dependent manner, resulting in an early peak of phosphorylation at 3 to 10 min, which then rapidly decreased to a near basal level. Pretreatment with PD 098059 reduced hepatocyte growth factor-mediated cell proliferation and urokinase-type plasminogen secretion. In contrast, SB 203580 pretreatment enhanced cell proliferation and urokinase-type plasminogen secretion due to induction of ERK phosphorylation. Treatment with PD 098059 and SB 203580 resulted in a decrease in phospho-ERK activity. Stable expression of dominant negative-MEK1 in HepG2 cells showed a decrease in hepatocyte growth factor-mediated urokinase-type plasminogen secretion.

Conclusions. Such results suggest that interaction of an MEK/ERK and a p38 kinase might be critical in intrahepatic invasion and metastasis of human hepatoma cells.

Key words: *hepatocyte growth factor, metastasis, mitogen-activated protein kinase, urokinase plasminogen activator.*

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