Different signaling pathways of cholangiocarcinoma

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Overexpression of receptor tyrosine kinase Met has frequently been found in cholangiocarcinoma. A research group in Thailand demonstrated that hepatocyte growth factor, a Met ligand, induced invasion and motility and altered E-cadherin localization in two cholangiocarcinoma cell lines, without having any significant effects on levels of two secreted matrix metalloproteinases. However, the signaling pathways underlying HGF-induced invasiveness of the two cell lines were different.

Cholangiocarcinoma (CCA), a bile duct cancer, is one of the major cancers in Northeast Thailand. This cancer is difficult to diagnose and has high metastatic and mortality rates. Overexpression of Met, a hepatocyte growth factor (HGF) receptor, has frequently been found in CCA and is correlated with progression of this type of cancer. HGF/Met activation induces a variety of cellular processes, including cell scattering, invasion and proliferation. Although a number of studies have been reported regarding the correlation between Met expression and CCA, the molecular mechanisms by which HGF induces CCA invasion are not completely understood.

A research article published on February 14, 2010 in the World Journal of Gastroenterology addresses this question. The research team led by Dr. Suthiphongchai T from Mahidol University used two CCA cell lines overexpressing Met, KKU-M213 and HuCCA-1, to study the role of Met in CCA invasion by activating the Met pathway with HGF. HGF strongly induced invasion and motility of the two CCA cell lines and concomitantly altered E-cadherin localization from membrane to cytosol, but did not affect the levels of secreted MMP-2, MMP-9 or uPA.

Signaling pathways responsible for HGF-induced invasion were further investigated. HGF induced ERK and PI3K/Akt pathways of both CCA cell lines but with different kinetic profiles. HGF induced sustained ERK activation in the KKU-M213 cell line, but transient ERK activation in HuCCA-1 cells. Using specific inhibitors of PI3K and ERK pathways, it was shown that HGF-induced invasion of KKU-M213 was strongly inhibited by both inhibitors, while that of HuCCA-1 was strongly inhibited by PI3K inhibitor but only weakly inhibited by ERK inhibitor. Thus, the signaling pathways responsible for HGF-induced invasiveness of the two CCA cell lines were different, in that PI3K pathway was common for both cell lines, whereas the role of ERK1/2 was likely to be dependent on the duration of ERK1/2 activation.

These results provided more information on the understanding of the signaling mechanisms responsible for HGF-induced CCA invasiveness, which may be helpful for identifying better targets for CCA therapy and for designing appropriate therapeutic strategy to suit each individual patient.

More information: Menakongka A, Suthiphongchai T. Involvement of PI3K and ERK1/2 pathways in hepatocyte growth factor-induced cholangiocarcinoma cell invasion. World J Gastroenterol 2010; 16(6): 713-722. www.wjgnet.com/1007-9327/16/713.asp

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