Research Grant, Interim Report

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Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma, accounting for approximately 10-15% of primary liver cancer. Although effective new treatments have increased survival for many other forms of cancer during the past 30 years, treatment strategies and survival for patients with intrahepatic cholangiocarcinoma have not improved. Still worse, patients affected by this deleterious disease respond poorly to aggressive chemotherapy or radiotherapy. Thus, identifying effective treatment strategies to improve patient survival and outcome is one of our major challenges.

The goal of our laboratory based at the Institute of Hepatology London is to understand the molecular mechanisms by which oncogenic signals regulate cholangiocarcinoma cancer cell proliferation. A specific focus of our studies is to understand how Mitogen-activated protein kinases (MAPK) signalling pathways regulate the function of downstream molecules involved in the progression of apoptosis, proliferation and oncogenic transformation of intrahepatic cholangiocarcinoma cells (**Figure 1**). Making use of genetic and cellular biology approaches with molecular and biochemical techniques, we are currently identifying and characterizing components of the MAPK signalling pathway involved in the development of cholangiocarcinoma. The findings from this work will allow a better understanding of how the MAPK pathway function in this cancer setting, and the ways they can be manipulated for controlling gene expression in cholangiocarcinoma cells.

MAPK are a family of widely expressed serine-threonine kinases regulating important cellular processes. MAP kinases participate in kinase cascades leading to the activation of three major MAPK family subgroups: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK) and the p38 group of protein kinases.

With the support of a ***Research Grant from the AMMF Cholangiocarcinoma Charity***, we were able to originate this project and, after one year of intense work, we are very excited in reporting that we have identified a novel protein JDP, a downstream effector of the MAPK cascade, that is highly expressed in 64.3% (9/14) of intrahepatic cholangiocarcinoma patients (**Figure 2**). Strikingly, elevated expression of JDP transcripts was also observed in two independent cohorts of human intrahepatic cholangiocarcinoma compared to their normal liver tissue. We found that, the expression of JDP mRNA was significantly higher than that in normal biliary epithelial cells (**Figure 3A**). Likewise, we also observed significantly higher expression of JDP in intrahepatic cholangiocarcinoma samples compared to their adjacent nontumor tissues (**Figure 3B**).

Altogether our preliminary data suggest that JDP may represent a target for ICC treatment. Further studies are however compulsory to understand how JDP promote ICC development in order to device specific inhibitors for JDP.

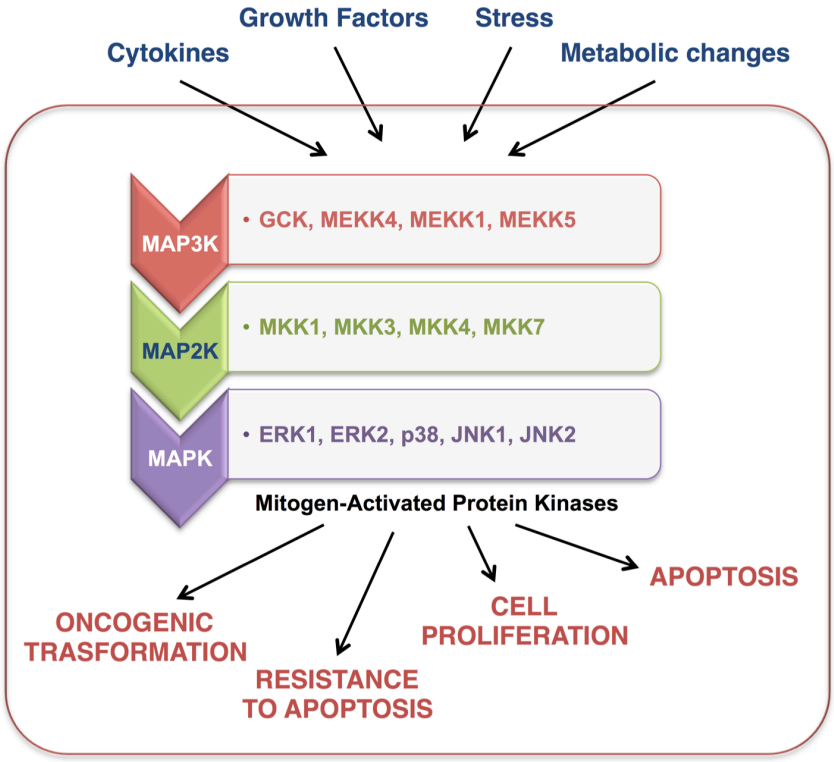

Figure 1. Schematic representation of the MAPK signalling pathway. Mitogen-activated protein kinases (MAPK) are a family of widely expressed serine-threonine kinases regulating important cellular processes. MAP kinases participate in kinase cascades leading to the activation of three major MAPK family subgroups: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK) and the p38 group of protein kinases. Deregulation of kinase activity has emerged as a major mechanism by which cancer cells evade normal physiological inhibition of growth and survival. Major efforts in cancer treatment are directed toward the identification and development of selective small molecule inhibitors of kinases implicated in cancer.

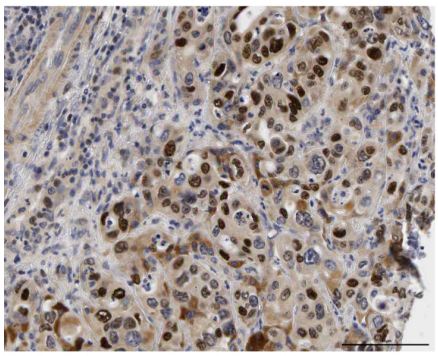

FIGURE 2. Expression of JDP protein in human ICC biopsies. JDP immunostaining of tissue microarray comprising 14 ICC livers. Shown are representative images of the immunostainings at 20x magnification.

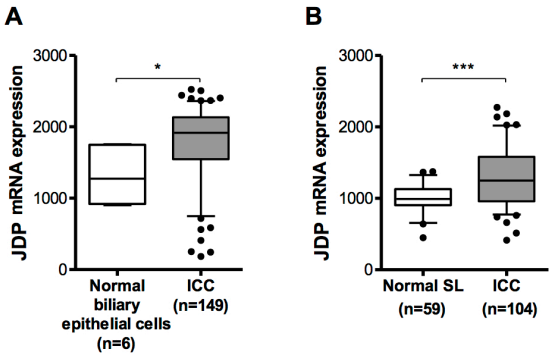

FIGURE 3. Expression of JDP mRNA in human ICC biopsies. Gene-expression analysis of JDP transcripts in ICC patients showing significantly higher expression of JDP in tumor tissues compared to normal biliary epitheleial cells (**A**) or surrounding non-tumor liver tissues (**B**). P values were calculated by nonparametric Mann-Whitney test. *P<0.05; ***P<0.0001