Molecular and Genetic Alterations of Hepatocellular Carcinoma

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Liver cancer (hepatocellular carcinoma, HCC) is a major malignancy in the world and is particularly prevalent in this region, being the second commonest fatal cancer in Southeast Asia including Hong Kong. Knowledge of the molecular and cellular targets underlying the development and progression of liver cancer is of importance as this can provide novel opportunities for prognosis and therapeutic interventions for this cancer.

Hepatitis B virus (HBV) infection is a major cause of HCC in Southeast Asia and Hong Kong. Using RNA interference (RNAi), we have shown that RNAi targeting HBx could reduce the HBx mRNA and protein levels in HCC cells and reduce HCC cell growth as well as tumor development in nude mice. Additionally, we have found that nuclear factor kappaB (NF-kB) activation was induced by HBx transfection in HCC cells through IkappaB kinase beta (IKK beta). HBx upregulated uPA and enhanced cell invasion synergistically with IKKbeta. We have also found that NF-kB activity was significantly increased in HBx-positive HCCs. uPA transcript was also upregulated in HCC, particularly in human HBx-positive HCCs and in those with NF-kB activation. Furthermore, activation of NF-kB and uPA was associated with more aggressive tumour behaviour. Activation of NF-kB and uPA upregulation leads to enhanced cell invasion and confer more aggressive tumour behaviour in HBx-positive HCC.

In HCC, recurrent chromosomal changes are common and they include loss of 1p, 4q, 8p, 13q, 16q, and 17p, and gain of 1q, 8q, and 20q. Chromosomes 8p and 13q have been shown to have frequent deletions in solid tumours and we have shown them to be among the most frequently affected chromosomes in HCC. Further detailed deletion mapping on these chromosomal arms can give important insight in the pathogenesis of this cancer. In the pursuit of identification of novel and important genes in HCC, we have previously isolated/ characterized two closely related genes, DLC1 and DLC2 (deleted in liver cancer 1 and 2), located on chromosome 8p and 13q, respectively, and encoding GTPase-activating proteins. They are candidate tumour suppressor genes and play important roles in hepatocarcinogenesis. We have found that the two chromosomal locations are frequently deleted in HCC and provided the evidence that DLC1 and DLC2 are frequently deleted in HCC. We have established that the genes exert significant cell growth inhibition in HCC cells. Furthermore, we have shown that the CpG island 5' to DLC1 is frequently methylated in HCC cell lines and human HCCs, contributing to transcriptional silencing of the gene. Additionally, our biochemical analysis indicated that both DLC1 and DLC2 proteins had GAP activity specific for small GTPases RhoA and Cdc42. Expression of the GAP domain of DLC2 sufficiently inhibited Rho-mediated formation of actin stress fibers, and suppressed Ras signaling and Ras-induced cellular transformation in a GAP-dependent manner. Taken together, our findings suggest that DLC1 and DLC2 may play an important role in growth suppression and hepatocarcinogenesis.