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TUMOUR SUPPRESSOR

Confirming DLC1

Hepatocellular carcinoma (HCC) is a chemoresistant cancer and a leading cause of cancer-related mortality, yet little is known about its causative molecular defects. Scott Lowe and colleagues have identified how deleted in liver cancer 1 (*DLC1*) on chromosome 8p functions as a tumour suppressor.

A survey of copy number alterations in HCC using representational oligonucleotide microarray analysis (ROMA) identified heterozygous deletions involving the *DLC1* locus in 59 of 86 tumours, consistent with previously published findings. *DLC1* mutations were also observed at a high frequency in human lung, colon and breast cancers.

To investigate whether loss of DLC1 was important for HCC development, the authors took *Trp53*-null mouse hepatoblasts co-expressing exogenous *Myc* (*Trp53*$^{-/-}$;*Myc*), which are able to form small tumours in mice, and knocked down *Dlc1* expression using microRNA-based short hairpin RNAs (shRNAs). When introduced into the spleens of recipient mice and allowed to 'seed' to the liver, *Dlc1*-knockdown cells accelerated the formation of liver tumours, which closely mimicked aggressive human HCC. Conversely, the introduction of ectopic *Dlc1* into hepatoma cells co-expressing oncogenic Ras resulted in dramatically reduced liver tumour formation compared with control cells. Taken together, DLC1 loss, when combined with other oncogenic lesions, is a driving force in the establishment of HCC.

DLC1 is a RhoGAP protein that limits cellular levels of active RhoGTP by catalysing its conversion to the inactive RhoGDP. Was DLC1 also acting through Rho in this context? Knockdown of *Dlc1* resulted in increased levels of activated RhoGTP in *Trp53*$^{-/-}$;*Myc* hepatoblasts. Furthermore, ectopic expression of a constitutively active RHOA mutant (RHOA^{V14}) in the same *Trp53*$^{-/-}$;*Myc* cells accelerated tumour formation when introduced into the livers of recipient mice. Significantly, shRNA-mediated suppression of *Rhoa* in murine hepatoma cells with attenuated DLC1 levels severely compromised their ability to form tumours in nude mice, and *Dlc1* knockdown rendered cells exquisitely sensitive to inhibitors of ROCK, an important downstream effector of RHOA. Together, these data indicate that inappropriate activation of RHOA as a result of reduced DLC1 expression is crucial for tumorigenesis in HCC.

Given the high incidence of DLC1 mutations in cancer, this study opens up the possibility of using inhibitors of Rho effectors as a therapeutic option in HCC.

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ORIGINAL RESEARCH PAPER Xue, X. *et al.* DLC1 is a chromosome 8p tumor suppressor whose loss promotes hepatocellular carcinoma. *Genes Dev.* **22**, 1439–1444 (2008)
FURTHER READING Farazi, P. A. & DePinho, R. A. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nature Rev. Cancer* **6**, 674–687 (2006)