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LIVER CANCER

IGF2 — an epigenetic oncodriver in HCC

Overexpression of insulin-like growth factor 2 (IGF2), mediated by epigenetic mechanisms, drives tumorigenesis in some hepatocellular carcinomas (HCCs), according to new research.

HCC is a substantial cause of global mortality. The only approved systemic treatment for patients with late-stage HCC is sorafenib, and research efforts in the past decade have sought to uncover genetic alterations associated with the disease, with a view to defining new druggable targets. However, less is known about the epigenetic landscape of HCC. Expression of IGF2, which is paternally imprinted, is known to be markedly upregulated in some HCCs, and epigenetic mechanisms could be responsible for these changes.

To define the role and mechanisms of IGF2 dysregulation in HCC, Josep Llovet and colleagues analysed 228 tumour samples from patients with the disease, as well as 168 paired non-tumour adjacent cirrhotic tissue samples and 10 normal liver samples from patients without HCC. Samples from tumours showed increased *IGF2* mRNA levels compared with non-tumour samples; importantly, tumours with high *IGF2* expression (>20-fold increase versus normal liver samples) had greater hypomethylation of promoters typically only active in fetal tissue than samples with lower *IGF2* expression (<20-fold increase). In human HCC cell lines with low *IGF2* expression and high fetal promoter methylation, forced demethylation of these promoters resulted in *IGF2* overexpression.

Using genetically engineered mouse models of HCC, the researchers found that *Igf2* overexpression accelerated tumour progression and decreased survival. However, liver-specific overexpression did not promote tumour initiation, suggesting *Igf2* is not a transforming oncogene in HCC.

Laura Marshall/NPG

Given the overexpression of IGF2 in human HCCs and evidence of its tumorigenic action, Llovet and colleagues assessed whether a monoclonal antibody (BI 836845, also known as xentuzumab) against IGF1 and IGF2 might have therapeutic potential. Mice with xenograft HCC tumours were given an inactive control, sorafenib, xentuzumab or a combination of both active compounds. Compared with standalone sorafenib or control compound treatment, xentuzumab alone or in combination with sorafenib reduced tumour growth and prolonged survival.

"There are two direct implications of this work," concludes Llovet. "First, to test xentuzumab in clinical proof-of-concept trials in HCC. Second, to explore the ideal biomarker to identify the subpopulation who might benefit from this drug."

Hugh Thomas

ORIGINAL ARTICLE Martinez-Quetglas, I. *et al.* IGF2 is upregulated by epigenetic mechanisms in hepatocellular carcinomas and is an actionable oncogene product in experimental models. *Gastroenterology* http://dx.doi.org/10.1053/j.gastro.2016.09.001 (2016)