Nature Reviews Gastroenterology & Hepatology | Published online 2 June 2016; doi:10.1038/nrgastro.2016.95

LIVER CANCER

A new drug target for hepatocellular carcinoma

> Our work identifies for the first time a MYC–AURKA complex as a therapeutic target in p53-altered liver cancer

The oncoprotein MYC is involved in the genesis and maintenance of many solid tumours, including hepatocellular carcinoma (HCC). Although previously considered undruggable, new findings now demonstrate that, in p53-altered liver cancer, MYC can be targeted through an interaction it forms with aurora kinase A (AURKA), suggesting potential for novel therapeutic strategies.

MYC is a multifunctional transcription factor with a critical role in signalling networks that are frequently activated in human solid tumours. As such, MYC is an attractive target for antitumour therapeutics but its molecular structure lacks cavities to which small molecules can bind, impeding the design of direct inhibitors. An alternative inhibitory strategy is to indirectly target MYC through complexes it forms with other proteins. In neuroblastoma, MYCN (closely related to MYC) was found to form complexes with AURKA that could be therapeutically disrupted. However, it was unknown whether AURKA complexes are formed in solid tumours in which MYC is the oncogenic driver.

HCC is one of the most frequently occurring solid tumours with a particularly dismal prognosis in a subset of patients who have genetic alterations in *TP53*, which encodes the tumour suppressor protein p53. "My laboratory is applying direct shRNA [short-hairpin RNA] screening technology to functionally identify new therapeutic targets in liver cancer," reports author Lars Zender. "We initially set out to use *in vivo* shRNA screening to mechanistically dissect the p53 pathway in liver carcinogenesis."

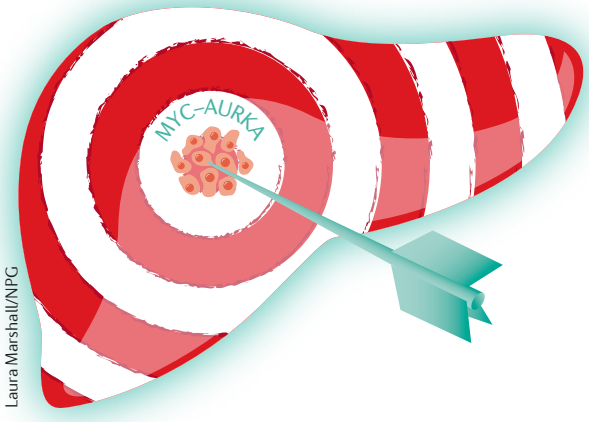
Interestingly, the authors first observed that p53-altered liver cancer cells, driven by the oncoprotein NRAS, need to overcome an AURKA-mediated cell cycle arrest before tumorigenesis, suggesting a tumour suppressing function for AURKA during HCC development. As the majority of HCCs develop in the context of chronic liver damage and regeneration — in which MYC is a key proliferation factor — the investigators then examined whether liver regeneration would allow an escape from the cell cycle arrest.

Using an *Nras*-activated, p53-altered mouse model of HCC, high expression levels of MYC were found in tumours after induced chronic liver damage, and strong tumour development was observed after delivery of *Myc*-expressing transposons. Together, these findings suggest that liver regeneration in p53-altered hepatocytes offers an escape from AURKA-induced cell cycle arrest via MYC. Indeed, an interaction between AURKA and MYC was found in p53-altered human and mouse HCC cells, suggesting that MYC expression levels are stabilized by binding with AURKA, over-riding the antitumour function of AURKA. Disruption of this interaction using inhibitors that changed the conformation of AURKA prevented the *de novo* formation of MYC–AURKA complexes, and induced the proteasomal degradation of MYC.

"The identification of this link between p53 inhibition, NRAS activation, MYC action and AURKA binding is novel and represents a significant advance in our understanding of the mechanisms underlying development and growth of liver cancer," says Lewis Roberts (Mayo Clinic, USA), who was not involved in the latest study. Furthermore, a strong correlation between *TP53* status and AURKA mRNA levels was found in human HCC samples, and treatment with an AURKA inhibitor (MLN8237) suppressed the growth of *TP53*-altered, but not wild-type *TP53*, human HCC cells. Additionally, in xenografts of *TP53*-altered human HCCs, the same AURKA inhibitor caused tumour remission and an almost complete suppression of tumour growth, demonstrating the therapeutic efficacy of AURKA inhibitors for a subgroup of patients with HCC.

"Our work identifies for the first time a MYC–AURKA complex as a therapeutic target in p53-altered liver cancer," explains Zender. "With MLN8237, a fully developed drug is available and therefore it should be possible to initiate a phase I/II trial relatively fast," he adds. The team also plan to test whether other solid tumours depend on a MYC–AURKA complex for their survival.

Iain Dickson



Laura Marshall/NPG

ORIGINAL ARTICLE Dauch, D. *et al.* A MYC-aurora kinase A protein complex represents an actionable drug target in p53-altered liver cancer. *Nat. Med.* http://dx.doi.org/10.1038/nm.4107 (2016)