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LIVER CANCER

The promise of new approaches in the management of hepatocellular carcinoma—adding to the toolbox?

Liver cancer is the third most common cause of cancer-related mortality, with >80% of liver cancer cases classified as hepatocellular carcinoma (HCC). Despite surgical and medical interventions being available, the prognosis for patients with HCC is ultimately poor —mostly as a result of late diagnosis. Now, findings from two research papers add new tools to the fight against HCC.

In the first study, published in *Proceedings of the National Academy of Sciences of the USA,* Mitchell Ho and colleagues investigated the potential of therapeutic antibodies for HCC. As such antibody-based therapies are available for other types of cancer, they reasoned that this approach might also be useful for liver cancer.

In recent years, glypican-3 (GPC3) has emerged as both a diagnostic biomarker and a candidate therapeutic target in HCC. GPC3 is expressed abundantly in HCC tissue, but not in healthy liver tissue; however, its biological function and role in tumorigenesis remain unknown. Investigations of several humanized mouse monoclonal antibodies against GPC3 are already underway. Adding to this body of work, Ho and co-workers sought to identify human anti-GPC3 monoclonal antibodies with therapeutic potential that directly inhibit HCC cell proliferation.

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A human antibody domain phage library was generated and, by screening this library, the investigators were able to identify a high-affinity human heavy-chain variable domain antibody against GPC3, termed HN3. Upon further analysis, HN3 was confirmed to bind to a specific GPC3 epitope that encompassed binding to both the N-terminal and C-terminal domains.

HN3 inhibited proliferation of GPC3-positive HCC cells *in vitro* and inhibited the growth of HCC tumours in mice *in vivo.* Insights into the underlying mechanisms of action of HN3 were also gleaned—this antibody purportedly acts by inducing cell-cycle arrest at G1 phase via Yes-associated protein signalling.

"The key technology we used in this work is single-domain antibodies", says Ho, who adds that a major advantage of these types of antibodies is their ability to target cryptic epitopes on tumour antigens. The researchers are continuing preclinical testing of HN3, and with the continued support of the National Cancer Institute, hope that this antibody can move forward to clinical trials as a treatment for liver cancer.

In the second study, published in *Hepatology*, Jeffrey Idle and colleagues from Switzerland and France combined metabolomics and transcriptomics to investigate how energy metabolism might be altered in HCC, given that the "liver is the principal metabolic engine of the body". As few therapeutic options are available for HCC, Idle reasons that "new treatments will surely come from a better understanding of the pathophysiology of HCC". "Major differences in energy metabolism between tumour and nontumour parenchyma are likely to be exploitable therapeutically," he adds.

First, 31 pairs of HCC tumours and corresponding healthy liver tissue from the same patients were analysed using GCMS (gas chromatography–mass spectrometry). Relative to nontumour liver tissue, HCC tumours were characterized by ~twofold depletion of certain energy metabolites (including, among others, glucose and malate), which was estimated as a fourfold increase in aerobic glycolysis over mitochondrial energy production in HCC cells (Warburg effect).

Next, a second panel of 59 HCC tumour samples that had been typed by transcriptomics and classified into subgroups G1–G6 (each with a distinct profile) was also analysed by GCMS. Notably, G1 (typical features include high levels of α-fetoprotein) and G3 (typical features include *TP53* mutations without HBV mutation) subgroups were associated with upregulated fatty acid catabolism.

The investigators plan to characterize the metabolic profile of further HCC samples in a much larger study. Idle is hopeful. "We remain optimistic that the worldwide rapid development of metabolomics will ultimately contribute to the characterization of novel molecular targets [for HCC] that could be exploited therapeutically," says Idle. "This is how we envisage potential victories in the battle against the scourge of liver cancer."

Although these studies are at an early stage, both approaches are promising developments that make tentative steps forward towards the ultimate goal of improvements in HCC treatment.

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Original articles Feng, M. *et al.* Therapeutically targeting glypican-3 via a conformation-specific single-domain antibody in hepatocellular carcinoma. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1217868110 | Beyoğlu, D. *et al.* Tissue metabolomics of hepatocellular carcinoma: tumor energy metabolism and the role of transcriptomic classification. *Hepatology* doi:10.1002/hep.26350