DKK1 as a serum biomarker for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis secondary to chronic alcoholism (1). Etiological factors for HCC vary widely depending on geographic location. In regions where Hepatitis B (HBV) is endemic, such as the eastern hemisphere, this is uniformly the most common cause (2). It is estimated that chronic HBV and hepatitis C virus (HCV) infections account for an estimated 78% of global HCC cases (3).

It has been widely established that the early detection of HCC enables more treatment options and translates to improved survival (4). Current American Association for the Study of Liver Diseases (AASLD) guidelines recommends the use of ultrasound for screening (5). Markers such as α-Fetoprotein (AFP) has long been used as a biomarker for HCC however often levels are related to vascular invasion and tumor burden and therefore can manifest late in presentation or sometimes not at all. The presence of AFP is not entirely specific to HCC and is often seen in situations of chronic benign liver disease and furthermore the most sensitive cut-off value by ROC analysis has been a topic of great debate. The need for a more sensitive and accurate screening tool in HCC has led to the emergence of various tumor biomarkers including microRNAs, osteopontin, & intermedin to name a few (6-9).

In a recent issue of *The Lancet Oncology*, Shen *et al*. designed a large-scale, multicenter validation study to assess the diagnostic accuracy of Dickkopf-1 (DKK1) as a serum protein marker for HCC (10). The authors have previously shown that DKK1 is overexpressed in HCC tissue but is not detectable in corresponding non-cancerous liver tissue, making this an attractive screening tool candidate (11,12). In

their current analysis the authors enrolled 1,284 participants including a test cohort of 424 HCC patients and 407 controls (213 healthy controls, 98 with chronic HBV, and 96 with liver cirrhosis). They compared results with a validation cohort (N=453) at a different institution.

Methodologically the authors analyzed serum DKK1 levels by receiver operating characteristics (ROC) to determine adequate cut-off values to determine validity of this as a screening adjunct. ROC curves showed the optimum diagnostic cutoff was 2.153 ng/mL [area under curve (AUC) 0.848 (95% CI, 0.820-0.875), sensitivity 69.1%, and specificity 90.6% in the test cohort; 0.862 (0.825-0.899), 71.3%, and 87.2% in the validation cohort]. They elegantly validate their findings which show that DKK1 alone or in combination with AFP was better than AFP alone. Previous cross sectional ROC studies of AFP as a screening tool (at various cut-off values) have shown sensitivities between 25-65% and specificities between 79-95% (13). Although impressive in sample size Shen *et al*., seem to echo prior results rather than offer a more accurate and practical alternative.

Where DKK1 may have a substantial role is in patients where AFP levels are negative or equivocal such as the case in chronic liver disease. The authors addressed this by examining AFP-negative patients and those with early HCC. They convincingly show that raised concentrations of DKK1 in serum could differentiate HCC from chronic HBV infection and cirrhosis, and that DKK1 and AFP together improved diagnostic accuracy for HCC versus all controls compared with either test alone.

What the authors fail to address is how specific is DKK1 to HCC? DKK1, a secreted protein, is known as a negative regulator of the Wnt signaling pathway. DKK-1 is reported

to be over expressed in many malignant tissues including breast cancer, lung cancer, esophageal carcinomas, ovarian and gastric cancer and previous groups have reported its potential use as a biomarker (14). (Not the main weakness of AFP) This lack of specificity detracts from the overall benefit of using DKK1 as a serum biomarker and mirrors some of the same issues that plague AFP in the first place.

In summary the use of DKK1 as a serum biomarker for the presence of HCC seems plausible based on work by Shen *et al.*, but it is unclear whether this has an advantage over well established markers of similar accuracy. The authors stated interpretation that DKK1 *could* complement measurement of AFP in the diagnosis of HCC and improve identification of patients with AFP-negative HCC and distinguish HCC from non-malignant chronic liver diseases is not challenged. What remains unclear is the exact role DKK1 will play as an adjunct, in what populations, and with what end-points in mind. Looking forward further studies should continue to examine and validate this promising screening tool, perhaps in western populations with analysis of its effect on long-term survival. This would be in line with universally accepted guidelines for the development of appropriate screening markers in oncology.

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