Who will be the next rising star? ——Any hope to find a reliable biomarker for HCC?

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Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and particularly prevalent in Mainland China, Southeast Asia and sub-Saharan Africa (1,2). HCC is the third most common cause of cancer-related death worldwide. It is due to the fact that most patients with HCC are often present at an advanced stage of the disease with intrahepatic or distant metastases, making surgical resection inoperable. In addition, the long-term survival of HCC patients after surgical resection is unsatisfactory, mainly due to a high incidence of tumor recurrence. Therefore, reliable biomarkers for detecting presence of HCC early and predicting recurrence early are of clinical importance in the management of HCC.

At present, alpha-fetoprotein (AFP) is the most commonly used serum tumor marker for HCC. It is still the standard tumor biomarker for HCC screening since its discovery. A serum AFP level greater than 400 ng/mL is considered highly suggestive of HCC in clinical practice. However, there is a significant portion of patients who have documented HCC but very low level of serum AFP. In some patients, high AFP is observed only in the early stages but the level then drops or even falls in the normal range as the disease progresses (3). All these cases will cause a false-negative diagnosis of HCC. In addition, some reports show that patients with non-malignant chronic liver diseases may give a false-positive result of diagnosis as some of these patients have high levels of AFP but without HCC (4). For this reason, serum AFP has been suggested to be more useful in detecting HCC with a non-viral etiology and it may have limitation in cases with a viral etiology (5). AFP can be further divided into 3 glycoforms (AFP-L1, AFP-L2 and AFP-L3). For clinical practice, AFP-L3, the major glycoform of AFP in the sera of HCC patients, can be used for prognostication purpose, as a high level of AFP-L3 is associated with poor cellular differentiation and larger tumor size of the tumor (6). To summarize, AFP has its limitations in specificity and sensitivity in the detection of HCC or its recurrence after treatment, especially in those patients with a viral etiology.

Biomarkers for HCC, other than AFP and its glycoforms, have been proposed. They include glypican-3 (GPC3), des-gamma-carboxy prothrombin (DCP), gamma-glutamyl transferase (GGT), golgi protein-73 (GP73) and a-fucosidase (AFU) [For review, please see (7-13)]. However, to our knowledge so far, none of them have satisfactorily high sensitivity, specificity and good prognostic power; each of them has their own advantages and limitations in detecting HCC in particular groups of patients when they are used alone. Therefore, it is logical to combine different serum markers with different diagnostic and prognostic significance and tackle such difficulties by combining their own advantages to fulfill the needs of clinical practice. In fact, many studies have successfully demonstrated the advantages of combining different biomarkers for HCC diagnosis and prognosis. For example, studies have shown that combination of AFP with other biomarkers, like GGT, GPC3 and DCP, may improve the overall sensitivity in detecting HCC (14-16). However, more clinical studies are needed to further establish the potential predictive significance of these combinations in clinical practice. Discovery of new potential biomarker(s) with high specificity, sensitivity and predictive power is still much awaited in HCC.

With the advancement of cellular and molecular techniques, many new potential biomarkers are being proposed and validated for their clinical significance

in diagnosis and prognostication in HCC. In a recent study, Shen *et al.* proposed a new potential biomarker Dickkopf-1 (DKK1) and validated its use in the diagnosis of HCC (17). DKK1 is a secretory protein and an antagonist of the canonical Wnt signaling pathway. It is well known that alternations of Wnt/β-catenin signaling pathway (canonical Wnt pathway) are closely associated with HCC formation (18-24). Recently, DKK1 has been proposed to be a potential biomarker in HCC by different groups (25-27). These studies have shown that DKK1 was up-regulated in both the tissue and serum samples of HCC patients. Its upregulation has been attributed to the hyperactivation of the canonical Wnt signaling pathway (25,27), as DKK1 is also a downstream target gene of the canonical Wnt signaling (28).

DKK1 has been reported to be a new potential biomarker in human HCC in several studies, however no large-scale and multicenter study has been done to further confirm and validate its clinical application in diagnosis until this recent study by Shen *et al.* (17). In that study, a total of 831 participants were used to determine the serum DKK1, including 424 HCC patients, 98 patients with chronic HBV infection (CHB), 96 patients with cirrhosis (LC), and 213 healthy controls. Their findings were further confirmed in a validation cohort with 453 participants consisting of 209 HCC, 73 CHB and 72 LC patients and 99 healthy controls. Therefore, this large-scale study with a total of 1,284 participants enrolled had a good power to assess the diagnostic relevance of serum DKK1 in human HCC. Furthermore, they showed that the optimal diagnostic cutoff of serum DKK1 for HCC detection was 2.153 ng/mL, as determined by the ROC curves from the test cohort. It had a sensitivity of 69.1% and specificity of 90.6% in detecting HCC. It was 71.3% and 87.2% in the validation cohort, respectively.

This study is of high significance and reveals serum DKK1 as a promising HCC biomarker. First, the authors have shown that serum DKK1 had a good diagnostic accuracy for early-staged HCCs, with solitary tumors of 2 cm diameter or less. Second, DKK1 was found to be a good biomarker in diagnosing HCC in AFP-negative patients, especially for patients with early-staged disease. Third, it had a significant power to distinguish HCC patients from patients with non-malignant chronic liver diseases. Therefore, serum DKK1 seems to be a more reliable biomarker for HCC diagnosis as compared with the AFP. Finally, the authors also demonstrated that a combination of AFP with DKK1 could further improve the diagnostic accuracy of HCC in their validation cohort. Overall, all these results have revealed that DKK1 is an important and significant serum biomarker for HCC.

In that study by Shen *et al.*, the authors established the role of DKK1 in HCC diagnosis and its advantages in combined use with the standard HCC biomarker AFP. However, they did not assess or report the role of serum DKK1 as a prognostic biomarker. The use of serum DKK1 as a prognostic biomarker has been shown by a previous study that upregulation of DKK1 was significantly associated with tumor recurrence and poor clinical outcome (25). Since tumor recurrence has great impact on patient survival in HCC, similar large scale studies with long-term follow up of HCC patients are much needed to confirm the role of DKK1 in predicting tumor recurrence for better clinical management.

Biomarker research is not only focused on establishing a diagnostic and prognostic marker for detecting early HCC and predicting the clinical outcome. In fact, numerous potential biomarkers in HCC are being evaluated with regard to their role(s) in personalized therapy. In fact, DKK1 may have a role as a potential functional biomarker in human HCC. Studies from Yu *et al.* and Tung *et al.* showed that knockdown of DKK1 by siRNAs reduced cell migration ability of HCC cells (25,27). Tung *et al.*, using in vivo animal model, further showed that DKK1 played a significant role in tumor growth. Therefore, further investigations of DKK1 as a therapeutic target for HCC patients are much awaited.

To conclude, a large-scale multicenter study from Shen *et al.* has shown that DKK1, a Wnt antagonist secretory protein, is a new potential biomarker for HCC diagnosis, especially in early HCC and AFP-negative patients. Interestingly, apart from its role as a diagnostic marker, more studies are needed to confirm its roles in prognostication and application as a therapeutic target for HCC treatment.

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