Serum Dickkopf-1 as a biomarker for the diagnosis of hepatocellular carcinoma

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Abstract: We reviewed the tumor markers for hepatocellular carcinoma, with special reference to the roles of Dickkopf-1 and α-fetoprotein in hepatocellular carcinoma

Key Words: α-fetoprotein; Dickkopf-1; hepatocellular carcinoma; receiver operating characteristic curve; tumor marker

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Liver cancer is the sixth most commonly cancer and the third leading cause of cancer death worldwide, with China alone accounting for more than 50% of the total (1). Hepatocellular carcinoma (HCC) is the most common form of liver cancer. HCC detected after the onset of symptoms has a dismal prognosis. The poor prognosis has been attributed to its insidious onset and late presentation at diagnosis. Effective screening systems to detect HCC at an early stage may result in more effective treatment and extend patient survival (2,3). However, the lack of symptoms in the early stage of HCC makes early diagnosis for HCC impractical.

Serum α-fetoprotein (AFP) remains the tumor marker universally utilized for diagnosis of HCC (3-6). The upper limit of normal AFP level in healthy adult was defined as 20 ng/mL (7), whereas the recommended diagnostic cut-off value for HCC is 400 ng/mL (3). It is well known that persistently elevated AFP levels are a high risk factor for HCC (4,5). AFP above 400 ng/mL can be considered diagnostic, but an AFP below 400 ng/mL does not exclude HCC, as up to 40% of HCCs will never produce AFP (3,8). To date, the diagnostic role of serum AFP in advanced HCC is well recognized. However, a serum AFP level greater than 400 ng/mL was found in only 2.4-22% of patients with small HCC (tumor size ≤3 cm) (5,8). In addition, a serum AFP level above 20 ng/mL was found in 33-65% of patients with small HCC (8). These shortcomings have limited its clinical application and detection of HCC. In addition, AFP may be elevated in nonmalignant liver disease (8-10). It is obvious that AFP alone is not a reliable indicator for the detection of HCC. Therefore, additional and more sensitive diagnostic tools must be sought.

The Wnt/β-catenin signalling pathway plays a pivotal role in development of both normal liver and hepatic carcinogenesis (11). Dickkopf-1 (DKK1) is an inhibitor of Wnt/β-catenin signalling and a downstream target of β-catenin (11). There is overexpression of DKK-1 in HCC cell line (10,12), tumor tissue and serum of patients with HCC (9,10,13). There is a stepwise increase in the serum DKK1 levels from hepatitis B virus (HBV)-associated cirrhotic patients to patients with early and HBV-associated HCC (10). Similar trends of increase of DKK1 transcript levels was also observed in the progression of HCC (10). Moreover, serum DKK1 level in HCC patients with cirrhosis was significantly higher than that in patients with cirrhosis alone (9). Moreover, the DKK1 level in HCC patients without cirrhosis was statistically higher than that in HCC patients with cirrhosis (9). This observation implied that elevated DKK1 level was, at least in part, not related to impaired liver function. Additionally, the DKK1

level was significantly reduced after liver resection (9,10). Therefore, elevated DKK1 level in patients with HCC was probably a result of over-production by the tumors (9,10). There was no significant correlation between serum levels of DKK1 and AFP (9,10,14). It is known that AFP level correlates with tumor size in advanced HCC (6). By immunohistochemistry, there is no correlation between DKK1-positivity and tumor size (≥5 *vs.* <5 cm) (14). However, there is correlation between serum DKK1 level and a larger tumor size (≥5 cm) (9,10). It is of note that this correlation disappeared when tumor size was less than 5 cm (9).

Serum AFP is identified as one of the most robust prognostic indexes in patients with HCC (15). AFP elevation contributes to increased risk for early recurrence and poor prognosis after curative therapy (5,6). However, a recent report indicated that AFP has no prognostic role in small HCC identified during surveillance in compensated cirrhosis (16). On the other hand, serum DKK1 level is a predictive marker of HCC invasiveness. Elevated expression of DKK1 in serum or transcript indicates poor clinical outcome, especially in early stage HCC and AFP-normal HCC (14). Furthermore, HCC patients with high DKK1 expression and high cytoplasmic/nuclear β-catenin accumulation had very poor prognosis (14). DKK1, used alone or in combination with β-catenin, is a novel prognostic predictor for HCC patients (10,14).

When used as a diagnostic test, AFP value of 20 ng/mL shows good sensitivity but low specificity, whilst the higher cut-off value of 200 ng/mL presents a high specificity but a sensitivity dropping to 22% (4). Recently, a ROC curve-identified AFP value of 100 ng/mL had good specificity (88%) but low sensitivity (23%) in small HCC (16).

To assess whether serum DKK1 level could increase the diagnostic accuracy for HCC, Shen *et al*. (9) reported a cross-sectional study using a test cohort (424 HCC patients and 407 non-HCC controls) and a validation cohort in another independent institute. The ROC analysis gave an optimal cutoff value of 2.153 ng/mL for DKK1, with a sensitivity of 69.1% and specificity of 90.6%. The area under the ROC curve was 0.848. They concluded that serum DKK1, alone or in combination with AFP, was better than AFP alone in the diagnosis of HCC (9). It is known that the diagnostic accuracy of AFP for small HCC is poor. In this study, the diagnostic accuracy of DKK1 in small solitary HCC (size ≤2 cm) showed no improvement compared with that of AFP when using all non-HCC subjects as a control, but the accuracy improved when using patients with non-HCC diseases as controls. In addition, there was no statistical difference in the level of serum DKK1 between AFP-positive and AFP-negative HCC. Moreover, the DKK1 level was not correlated with tumor size small than 5 cm. Accordingly, there was no definite evidence indicating that DKK1 was better than AFP in diagnosis of small HCC. In addition, HCC related to hepatitis C virus infection or heavy alcohol consumption has never been evaluated. Cholangiocarcinoma or metastatic liver cancer must also be investigated to rule out potential sources of false positive results. Hence, more studies needed to be performed before DKK1 can be accepted as a diagnostic tool for HCC.

Apart from AFP, several novel markers have been developed with the intent to improve the diagnostic power and to better detect HCC in the at-risk populations (4-6,9,10). These new biomarkers, used alone or in combination, increase diagnostic accuracy for HCC (5,6,8-10). However, they have not offered any substantial advantage with respect to AFP (4-6,17). To date, none of tests used for HCC detection can be recommended to survey at-risk populations for HCC development (17).

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