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Commentary

Development of Serum DHCR24 Antibody as a Marker for Hepatocellular Carcinoma: The End of the Beginning

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Looking for novel serum markers for early detection of hepatocellular carcinoma (HCC) has been a hot area of research for more than 20 years. Notwithstanding the intensive research efforts, there have been scanty serum markers with optimal performance for generalized clinical use. This is partly because HCC typically arises from the background of diseased liver with long standing cirrhotic and hepatitic changes, whereas few markers are specifically expressed in tumors without co-expression in non-tumorous tissue. HCC is also known to be a highly heterogeneous cancer, with different etiological, geographical and genetic compositions. As a result, it is difficult to identify a single marker suitable for all HCC patients. Taking alpha-fetoprotein (AFP) as an example, the sensitivity is approximately 70% in diagnosis of HCC but it becomes lower in the setting of surveillance for small sized tumor (Chan et al., 2014). In addition, AFP is limited by the false-positivity in patients with active hepatitis. As compared to hepatitis B virus (HBV) infection, this problem appears to be worse for hepatitis C virus (HCV) infection, which is characterized by variable degree of chronic active hepatitis. Although recent data indicate that the specificity of AFP could improve after treatment with effective anti-viral therapy which diminishes the hepatitis activity (Wong et al., 2014; Oze et al., 2014), it remains controversial whether serum AFP should be recommended for surveillance of HCC. To overcome above weaknesses, various serum markers for HCC have been tested with notable examples including Prothrombin Induced by Vitamin K Absence-II (PIVKA-II) and Lens culinaris agglutinin-reactive AFP (AFP-L3). These markers are associated with higher specificity in diagnosis of HCC, but at a cost of lower sensitivity (Sterling et al., 2009). As a result, none of them are considered very useful markers for surveillance of HCC.

In this issue of *EBioMedicine*, Ezzikouri et al. reported on the use of a novel serum marker, 3β-hydroxysterol Δ24-reductase auto-antibody (DHCR24 Ab), as a surrogate marker to indicate progression from chronic hepatitis C to HCC (Ezzikouri et al., 2015). By evaluating serum levels of the antibody in patients with different stages of disease, it was found that the concentration of DHCR24 Ab in the HCC cohort was higher than cirrhotic patients, while the levels in cirrhotic patients were higher than the hepatitis cohort and healthy subjects, respectively. In diagnosing HCC, the performance of serum DHCR24 Ab was better than AFP (cutoff at 20 ng/ml) and PIVKA-II (cutoff at 40m IU/ml) with higher sensitivity, specificity and area-under-curve (AUC) at the cutoff of 11.5 μg/ml. Further, DHCR24 Ab was elevated in more than 70% of patients who did not have elevation of AFP or PIVKA-II, and the combination of serum DHCR24 Ab with AFP and PIVKA-II had good sensitivity of higher than 87% in diagnosis of HCC. All of these phenomena were only observed in the HCV population but not in the HBV patients. The authors conclude that serum DHRC24 Ab is a potential marker for HCV-related liver disease and may facilitate the diagnosis of HCC.

The authors have to be congratulated for conducting such a large-scaled clinical study with sample size of more than 600 patients. This robust sample size has enabled statistical analysis of the diagnostic and prognostic performance of the novel marker in different stages and etiology groups of patients. We concur that the DHCR24 Ab is worthy of further investigations for potential clinical use in prognostication of severity and surveillance of HCC in patients with HCV infection. There are several areas in which the marker can be developed to match the need in real-world setting. First, a number of predictive models have already been developed to gauge the risk of progression of HCV infection, by incorporating multiple clinical factors, including AST/ALT ratio, bilirubin and albumin levels (Bonis et al., 1999; Ghany et al., 2010). It remains unclear whether serum DHCR24 Ab provides independent prognostication to those predictive models or clinical factors. Second, clinicians nowadays rely on abdominal ultrasonography for surveillance of HCC. Recent study suggested that the combination of serum marker AFP and abdominal ultrasonography could improve the effectiveness of HCC surveillance (Chang et al., 2015). Therefore, it is crucial to

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study the combination of serum DHCR24 Ab and abdominal ultrasonography in the surveillance of HCC. Third, only the serum sample collected at one single time point has been studied based on the belief that the antibody level is reflective of quantity of DHCR24 protein. Nevertheless, the production of antibody is prone to be influenced by other factors such as host's immunity and the presence of concomitant active infection. It is unclear whether any the antibody level fluctuates along the disease course of HCV infection, particularly after antiviral treatment. To address this question, future investigations should involve study on quantification of DHCR24 Ab in serial serum samples in the patient cohort. Fourth, DHCR24 participates in cholesterol synthesis with its blood level in close correlation with body weight, fast glucose level and HbA1c (Berisha et al., 2011). Hence, the potential applicability of serum DHCR24 Ab in prognostication of patients with non-alcoholic fatty liver disease, which is the commonest metabolic liver disease worldwide, should be explored.

In summary, the current study by Ezzikouri et al. has undoubtedly provided researchers a novel marker to work on, in particular for surveillance of HCC in HCV population. However, previous experiences of developing tumor markers have already taught us that HCC and HCV are both complex diseases. A lot more works are required to determine whether DHCR24 Ab represents a promising hope for patients.

Disclosure

The authors declare no conflicts of interest.

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