EBioMedicine 12 (2016) 4–5

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Serum TGF-β1: A Potential Biomarker for Early Detection of Hepatocellular Carcinoma

Jian He, Yang Liu *

Key Laboratory of Separation Science for Analytical Chemistry, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

ARTICLE INFO

Article history:
Received 19 September 2016
Accepted 19 September 2016
Available online 20 September 2016

Hepatocellular carcinoma (HCC) is a type of liver cancer, causing the highest mortality in the world (Hong et al., 2015). Although surgical operation or other intervention therapies are effective at an early stage of HCC, up to 70% of these early stage patients will develop to recurrent tumors within five years (Hong et al., 2015), suggesting that it is quite important to establish a promising biomarker for early diagnosis of the development of HCC.

Although considerable progress has been made in HCC biomarkers discovery, very few biomarkers have exhibited promising clinical outcome. AFP (alpha-fetoprotein), is currently being considered as a well-established biomarker for HCC, but the positive predictive value is estimated less than 33% (Chen et al., 2003). Furthermore, the association of AFP with ultrasonography only improved the sensitivity by around 7% and the specificity by only 2% compared to applying ultrasonography alone, while increasing the cost of the screening (Zhang and Yang, 1999). In addition, not only less than 20% (10–20%) portion of early stage tumors present with abnormal AFP serum levels (European Association for Study of Liver., 2012), but also high serum AFP level in cirrhosis patients could be caused by HBV or HCV infection, or exacerbation of other underlying liver diseases other than HCC (Di Bisceglie et al., 2005). These information above clearly demonstrated that AFP may not be a ideal biomarker for HCC diagnosis. The otherbiomarkers, such as DCP (des-γ-carboxy prothrombin), GPC3 (glypican-3), and GP73 (Golgi protein 73) (Yamamoto et al., 2010), have been proposed as early biomarkers for HCC, cannot stand for a criteria to assess the development of HCC. To date, none of these molecules are promising in predicting the risk of HCC occurrence and no effective systemic biomarkers have been established.

Predicting cancer occurrence by simple blood testing is most rapid and convenient way for early detection of human disease. However, many approaches to identify HCC biomarkers are based on NGS (next generation sequencing) technology (Li and Mao, 2013), which is costly and time-consuming. In a study published in this issue of *EBioMedicine*, Watanabe et al. (2016-in this issue) demonstrated that the serum level of TGF-β1 negatively correlates with HCC occurrence, suggesting the potential of TGF-β1 as a novel biomarker for HCC early detection v. TGF-β1 is one of three members of the transforming growth factor β superfamily of cytokines. It is a secreted protein involved in a number of cellular functions, including cell proliferation, cell growth, differentiation and apoptosis. Meindl-Beinker group revealed that TGF-β1 may function as a tumor suppressor at early stages of liver damage, whereas TGF-β1 may promote tumor associated phenotype rat cancer early stages (Meindl-Beinker et al., 2012). Moreover they also showed that TGF-β1 could function as a molecular switch of the pathway from cytostatic to tumor promoting in survival signaling pathways in hepatocytes. These findings suggest TGF-β1 be a novel therapeutic target for inhibition of liver disease progression (Meindl-Beinker et al., 2012).

In this present study, a nested case-controlled (NCC) study was employed as the statistics method (Watanabe Y et al., 2016-in this issue). Different from a case-control study, only a subset of controls from the cohort is compared to the incident cases in a NCC study (Cai and Zheng, 2012). In this NCC study, factors such as HCV infection were matched to selecting controls from relevant risk sets, which could be more efficient and reliable than a case control study with the same number of controls. Since little is known about the relationship between TGF-β1 related pathway and HCV-positive HCC, further study may be required to show the role of TGF-β1 in these individuals. Furthermore, an alternative interpretation for the decreased serum level of TGF-β1 is the enhanced uptake of TGF-β1 by liver tissue. Increase of cellular TGF-β1 may significantly contribute to the pathogenesis of HCC, thus, the intracellular level of TGF-β1 and pathological analysis in liver tissues may be of importance to be investigated in the future.

In conclusion, the study by Watanabe et al. (2016-in this issue) may open an interesting perspective of predicting biomarker and provides option for a diagnostic approach from blood samples of HCC. These finding would potentially contribute to improvement in prediction and early detection of HCC development.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.09.001.
* Corresponding author at: Scientific Research Center for Translational Medicine, Department of Biotechnology, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Rd, Dalian 116023, China.
E-mail address: yliuqq@dicp.ac.cn (Y. Liu).

http://dx.doi.org/10.1016/j.ebiom.2016.09.018

Disclosure

The authors declared no conflicts of interest.

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