EDITORIAL

Serum Protein Kinase C Delta: New Kid on the Block for Early Detection of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths in the world.[1] Age-standardized incidence rates of HCC are highest in Asia and Africa; however, both incidence and mortality are rapidly rising in the United States and Europe due to a shift in epidemiology of HCC from viral hepatitis to nonalcoholic fatty liver disease–related cancer.[2] Given the dual clinical challenges of detection at late stages and the high incidence-to-mortality ratio of HCC,[3] major hepatology societies have recommended abdominal ultrasound with or without alpha fetoprotein (AFP) as the primary HCC surveillance strategy for at-risk patients.[4] However, ultrasound suffers from low sensitivity for detecting early-stage HCC, with factors such as operator experience and patient factors, such as obesity, decreasing its diagnostic accuracy.[5–7] At present, only limited data exist on the cost-effectiveness of other imaging modalities, such as computed tomography and magnetic resonance imaging.[8,9]

Given the limitations of imaging-based strategies, serum-based biomarkers have an important role in HCC surveillance. AFP has been widely used in combination with ultrasound for HCC surveillance. AFP has significant limitations as a biomarker for the detection of HCC due to low specificity when used alone, but combining it with ultrasound improves sensitivity from 45% with ultrasound alone to 63% with ultrasound plus AFP.[5] However, it is obvious that no single serum biomarker may be sufficient due to HCC tumor heterogeneity and the need to predict response to therapy.[10] Thus, other serum biomarkers such as des-γ-carboxy prothrombin (DCP), GALAD (gender, age, AFP-L3, AFP, and DCP), and methylated DNA markers panel are being investigated in HCC surveillance strategies.[10–12]

In this issue of *Gastro Hep Advances*, Oikawa et al report on the potential of serum protein kinase C delta (PKC-δ) as a novel biomarker for HCC complementary to biomarkers currently used in clinical practice.[13] These investigators previously reported that while PKC-δ is an intracellular serine/threonine kinase, HCC cells secrete PKC-δ into the extracellular space, where it acts as a growth factor for HCC progression, while neither normal hepatocytes nor non-HCC gastrointestinal cancer cells secrete PKC-δ.[14] They also demonstrated that HCC patients had higher serum PKC-δ than patients with a chronic liver disease or healthy controls. Here, they extend their observations on serum PKC-δ in a larger group of patients with a chronic liver disease with or without HCC.

Serum PKC-δ levels were found to be higher in chronic liver disease patients with HCC than in those without HCC. They also report that in their cohort, the diagnostic performance of PKC-δ was comparable to that of AFP and DCP. However, a particularly intriguing observation is that serum PKC-δ levels were elevated in a subset of patients that were double-negative for AFP/DCP, and serum PKC-δ levels were not correlated with AFP/DCP levels. This finding suggests that serum PKC-δ may detect tumors with distinct biology and serve as a complementary biomarker to the GALAD, which includes both AFP and DCP.[15] A second observation that deserves further investigation is that serum PKC-δ performed better than AFP/DCP in detecting very early-stage (solitary and small) tumors.

Despite the promise serum PKC-δ holds as a biomarker of early-stage HCC, several questions need to be addressed before it can be adopted in clinical practice. First, this study will need to be replicated in a larger, more diverse group of patients. Second, given the rapidly changing epidemiology of HCC from a viral hepatitis-related to nonalcoholic fatty liver disease-related cancer, diagnostic performance of PKC-δ will need validation in subjects with and without coexisting obesity. Third, the role of serum PKC-δ as a complementary test to conventional biomarkers will need validation. Fourth, determining the diagnostic performance of serum PKC-δ levels in combination with abdominal ultrasound will be needed and compared with other emerging biomarker panels such as the GALAD score and circulating cell-free DNA. Fifth, the ability of PKC-δ to identify tumors with distinct biology and/or response to specific treatments will need additional exploration.

In summary, there is an urgent need to improve surveillance strategies for HCC, a common cancer with increasing incidence and high mortality, as the current strategy consisting of ultrasound with or without AFP has significant limitations. Serum PKC-δ represents a novel biomarker for HCC detection that may prove to be complementary to other serum biomarkers, particularly in cases of AFP/DCP double-negative tumors and in detection of small, early-stage HCC.

JAIDEEP BEHARI[1,2,3]
[1]Division of Gastroenterology
Hepatology and Nutrition
Department of Medicine
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
[2]Division of Cancer Control and Population Sciences
UPMC Hillman Cancer Center
Pittsburgh, Pennsylvania
[3]Pittsburgh Liver Research Center
University of Pittsburgh
Pittsburgh, Pennsylvania

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Correspondence:
Address correspondence to: Jaideep Behari, MD, PhD, Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, 3471 Fifth Avenue, Kaufmann Medical Building; Suite 201, Pittsburgh, PA 15213. e-mail: behajx@upmc.edu.

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