東京慈恵会医科大学
THE JIKEI UNIVERSITY SCHOOL OF MEDICINE

Press release

August 4th

The Jikei University School of Medicine

Serum PKCδ is a novel biomarker for early-stage of Liver Cancer

The Jikei University School of Medicine (Location: Tokyo, Japan) discovered that serum protein kinase C delta (PKCδ) Is a novel biomarker for early-stage of Hepatocellular carcinoma (HCC).

Recently, Dr. Kohji Yamada and his team reported for the first time that (1) PKCδ is specifically secreted into extracellular space in HCC cells, which was previously thought to exist in only cytoplasm, and autophagy is involved in this secretion mechanism, (2) PKCδ contributes to cell proliferation by activating Erk1/2 and STAT3 signaling via IGF-1R and EGFR, and (3) administration of anti-PKCδ antibody inhibits tumor growth (Cancer Res, 2021 81(2):414-425., Cancer Sci, 2022 113(7):2378-2385., PNAS *in press*).

The clinical usefulness of serum PKCδ as a biomarker for HCC diagnosis was confirmed by collaboration with Division of Gastroenterology and Hepatology (Dr. Tsunekazu Oikawa, Dr. Masayuki Saruta) and Core Research Facilities, Research Center for Medical Science (Dr. Akihito Tsubota) at Jikei.

PKCδ levels in HCC patients were significantly higher than those in healthy subjects and chronic liver disease (CLD, chronic hepatitis and liver cirrhosis), and approximately 40% of conventional tumor markers (AFP and DCP) double-negative HCC patients were positive for PKCδ.

The diagnostic performance of serum PKCδ to discriminate HCC patients from patients with chronic liver disease was comparable to that of AFP and DCP. Interestingly, PKCδ yielded better diagnostic performance for detecting solitary small-sized (≤20 mm, BCLC stage 0: very early-stage) HCC, compared to AFP and DCP.

Publication of this study

These findings were published in "***Gastro Hep Advances***" on the 4th August https://www.ghadvances.org/article/S2772-5723(22)00134-0/fulltext. This study was supported by the Japan Agency for Medical Research and Development (AMED).

Findings of this study

Liver cancer is the fourth leading cause of cancer-related death worldwide, and is known to be a common cancer with a poor prognosis. The only curative treatments for liver cancer are surgical resection and liver transplantation for early-stage patients. However, most patients are diagnosed at advanced stage by which time extant therapies are not ineffective. AFP and DCP are commonly used as conventional biomarkers for HCC, and their serum levels are elevated along with advanced HCC stages. Identification of an alternative biomarker that can detect early-stage and conventional tumor marker-negative HCC is urgently needed. This study aimed to assess the practical usefulness of serum PKCδ for detecting HCC in CLD patients. Serum PKCδ was measured in 9 healthy subjects, 126 patients with CLD, and 187 HCC patients by a sandwich ELISA to analyze the diagnostic performance for HCC and compare it with conventional markers.

Serum PKCδ in the HCC patients (median, 46.9 ng/mL) was significantly higher than that in healthy subjects (median, 27.0 ng/mL) and patients with CLD patients (median, 37.9 ng/mL) [P < 0.001]. ROC analysis of the diagnostic performance of serum PKCδ for HCC showed a cutoff value of 57.7 ng/mL, AUC 0.686, sensitivity 38.0%, specificity 97.3%, AFP >20 (AUC 0.641, sensitivity 29.6%, specificity 98.6%), DCP >40 (AUC 0.716, sensitivity 50.0%, specificity 93.2%), indicating that the diagnostic performance for HCC is comparable to that of conventional tumor markers. PKCδ, AFP, and DCP were independent of and complementary to each other, and the PKCδ-positive rate in the AFP(-) DCP (-) HCC was 42.5%, suggesting that PKCδ has unique characteristics differed from conventional markers. (Figure 1).

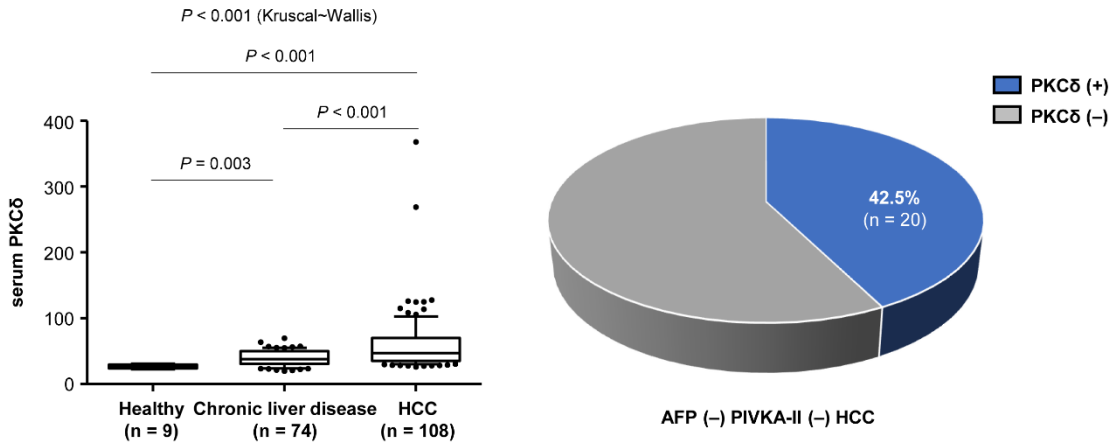

Figure 1. Serum PKCδ levels in HCC patients, non-HCC patients, and healthy subjects. There were significant differences in serum PKCδ levels among the three groups ($P < 0.001$ by the Kruskal–Wallis test) (right panel). The proportion of PKCδ-positive and -negative patients in the AFP/DCP double-negative group (left panel).

It is noteworthy that that PKCδ had the highest sensitivity, with a positive rate of 45.0% in HCC patients with a single and solitary small-sized (≤20 mm, BCLC stage 0: very early-stage). On the other hand, the positive rates of AFP and DCP were only 15% each, and even when AFP and DCP were used in combination, the diagnostic performance of PKCδ was not exceeded (Figure 2).

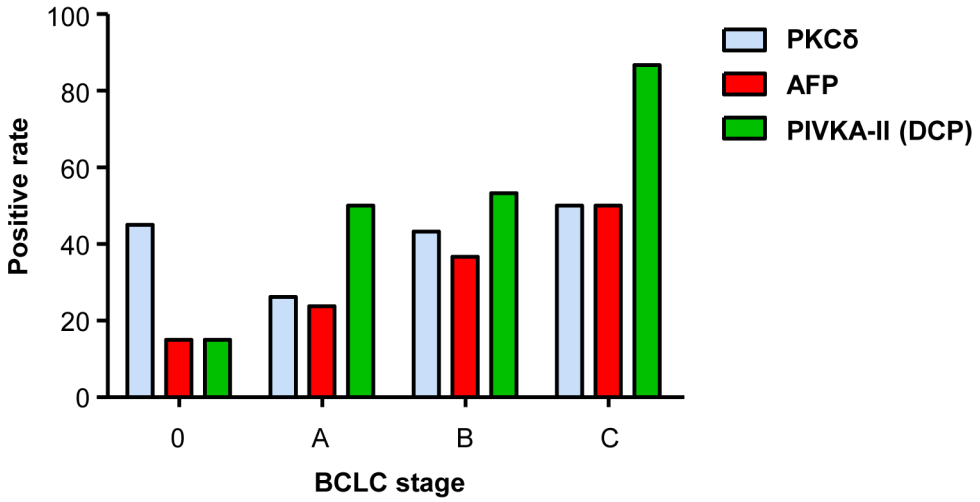

Figure 2. The positive rates of PKCδ, AFP, and DCP according to the BCLC stages. The PKCδ-positive rates were similar across all stages, whereas the AFP- and DCP-positive rates were significantly increased stepwise along with advanced HCC stages.

Furthermore, PKCδ had the highest AUC of 0.762 among the three markers. Therefore, serum PKCδ is a novel HCC biomarker, which is independent of and complementary to conventional markers. Specifically, PKCδ may be useful for detecting very early-stage or AFP/DCP double-negative HCC.

Future development

The sandwich ELISA kit used for the measurement of serum PKCδ is a research reagent. The team has been aiming at the development of diagnosis kit for measurement in clinical practice. Currently, the research with a title of "Establishment of novel biomarker targeting PKCδ in liver cancer" (principal investigator: Dr. Kohji Yamada) has been ongoing as Practical Research for Innovative Cancer Control Program by Japan Agency for Medical Research and Development (AMED).

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