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Dynamic pattern and terminal switch of lipid metabolomics in HBV tumorigenesis

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Background: The lipid metabolic disorders were frequently observed in patients of HBV and HCV-associated hepatocellular carcinoma (HCC). The underlying mechanism and significance remains to be clarified.

Aim: In this study, we attempt to clarify the role of lipid metabolism in HBV tumorigenesis.

Methods: The dynamic, temporal pattern of lipid metabolic profiles in serum and lipid were demonstrated in two transgenic mice models of HBx and pre-S2 deletion mutant by biochemistry and Affymetrix DNA array chip. The data were confirmed by western blot and further validated in human HCC tissues.

Results: We observed an interesting biphasic response pattern of lipid metabolomics in both HBx and pre-S2 mutant transgenic mice models of HBV tumorigenesis. The first peak of fatty change occurred in the early phase of 1-3 months, which subsided and then remarkably increased or terminally switched in HCC tissues. This biphasic pattern was synchronized with ATP citrate lyase (ACYL) activation, followed by the activation of sertol regulatory element binding transcription factor 1 (SEBPF1) and fatty acid desaturase 2 (FADS2) in pre-S2 model. In HBx model, five lipid genes were specifically activated at the terminal phase including the lipoprotein lipase, fatty acid binding protein (FABP). In both models, the endoplasmic reticulum (ER) stress-induced mTOR pathway is the driving signals. Such an ER stress-dependent mTOR signal cascade is also important for cell proliferation of hepatocytes and further validated in HCC tissues.

Conclusion: The mTOR signal pathway is important for the lipid metabolic disorders and the driving force for HBV tumorigenesis in animal and human models. To target on this pathway we will provide chemoprevention for HCC tumorigenesis in high risk patients of chronic HBV infection.

Biography

Su received his MD degree from National Taiwan University Medical School in 1976, and PhD degree in Pathology in 1987. His major research interest is virus and virus-associated human cancers. He was the pioneer investigator in EBV-associated T cell lymphoma, and was appointed as the member of International Lymphoma Study Group (1996-2008) for WHO lymphoma classification. During the SARS period, he served as the Director General of Taiwan CDC and successfully controlled SARS. In 2011-2013, he was appointed as the Director of National Institutes of Infectious Diseases and Vaccinology, NHRI to develop vaccines for EV71, H7N9, and BCG. In the past decade, he become interested in HBV carcinogenesis and identified pre-S2 mutants as the new viral oncoproteins, and ground glass hepatocytes as pre-neoplastic lesions. He studied the cancer metabolomics and started to apply these biomarkers, especially mTOR and c-myc signals, for chemoprevention of high risk chronic HBV carriers. He published a total of around 300 papers, many of which in the prestigious journals like *Lancet*, *Blood*, *Journal of Clinical Investigation*, *Hepatology*, etc. His many studies have been translated into clinical application and industry development.

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