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Stage evolution of lipidomics and gene expressions associated with metabolic syndrome in HBx transgenic tumorigenesis

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Hepatitis B virus (HBV) X protein (HBx) has been recognized as a viral oncoprotein and HBx transgenic mice develop a high incidence of hepatocellular carcinoma (HCC). The current notion on the linkage between metabolic syndrome and cancer drives us to explore the stage evolution of lipidomics and gene expression signatures associated with metabolic syndrome in HBx-transgenic mice livers at various stages of tumorigenesis. Histopathology revealed a consistent fatty change of livers at each stage, which progressed from fine cytoplasmic vacuoles at 1-6 months to a fatty nodule at 12 months, and finally early HCC with fatty change. Lipidomic analysis of liver tissues revealed a significantly higher level of cholesterol and triglyceride in tumor part. The expression profiles of gene clusters at different stages were then analyzed by Agilent mouse microarray. Candidate genes profiles of fatty acid biosynthesis (ALOX5, FADS2, LPL, PRKCA, SLC27A4 and SOAT1), accumulation of lipid (AGPAT9, APOB, AQP7 and FABP4 SCD2,), and lipid metabolism (MOGAT, OXCT1 and PITPNM1) were universally mildly activated at early stages, but stably activated at the advanced or tumor stages. Among which, arachidonate 5-lipoxygenase (ALOX5), fatty acid desaturase 2 (FADS2), protein kinase C, alpha (PRKCA) were specifically activated at the advanced stages, and were closely related to proinflammatory NFkB, CCL13 and TNF-a activation. Therefore, we propose a two-stage model for the relationship between metabolic syndrome and HBx tumorigenesis: the early stage of fatty change associated with general stress response and the second or advanced stage involving the activation of selected gene clusters associated with pro-inflammatory NFkB activation, fatty nodule formation and tumor development. These results provide useful information for understanding the role of inflammation and metabolic syndrome in HBV tumorigenesis.

Biography

Dr. Su served as chair professor and director of the Department and Institute of Pathology, NTUH and NCKU Hospital. His major research interests are on the pathogenesis and therapy of virus-associated human cancers. He identified the pre-S mutants in ground glass hepatocytes as the new viral oncoproteins in HBV hepatocarcinogenesis. Many of his discovery and basic researches have now come to the stages of clinical application. He has published a total of more than 240 SCI papers in journals such as Lancet, Lancet Infectious Diseases, BLOOD, Journal of Clinical Investigation, Hepatology, Am J Pathol, et al.