Extended Abstract Research & Reviews: Medical and Clinical Oncology 2020
Vol.4 No.1

Liver cirrhosis and hepatocellular carcinoma regulated by ERK signaling pathway

Chiung-Fang Chang
Researcher at Far Eastern Memorial Hospital, Taiwan

Chronic liver injury leads to cirrhosis, the fourteenth most cause of death worldwide. Patients with liver cirrhosis could develop hepatocellular carcinoma, one of leading malignancies. The liver injury in long term and liver cirrhosis results in immune responses and recruit many immune cells. In CD4 subsets, regulatory T cells (Treg) and T helper 1 (Th1) cells inhibit liver cirrhosis whereas T helper 2 (Th2) cells promote the process. The balance between different subsets and their interaction with damaged livers could change immune tolerance as well as have effects on the degree of liver injury. Both WT and Erk2 deficient mice were compared under Choline Deficient Ethioine-supplemented diet (CDE diet), which leads to liver injury. It is obvious that WT and Erk2 deficient livers changed their color into brownish, suggesting liver damage occurred. Tissue sections were subjected to histological analysis by H&E and TRI staining. Our data suggested that Erk2 deficient livers have less degree of cirrhosis than WT livers upon liver injury. However, the relative body weight of WT and Erk2 deficient mice were similar. Erk2 deficient livers also have lower expression in cirrhosis-related genes-SMA and Col1a1 in comparison with WT. Furthermore, Erk2 deficient hepatic CD4 T cells were less activated and had less expression in IFN Therefore, it is possible that down-regulation of MAPK signaling could slow down the process of liver cirrhosis. In HCC cell line, inhibition of Erk could induce apoptosis but did not alter cancer stem cell marker of CD133. In conclusion, ERK -regulation and short hairpin RNA–mediated down-regulation demonstrated the function of RN181 as a tumor suppressor because it decreased the proliferation and colony formation of HCC cells in vitro and inhibited tumor growth in vivo by suppressing cell proliferation and enhancing cell apoptosis in xenografted tumors. Proteomic analyses showed that RN181 regulates the expression of many proteins that are important in many cellular processes. Statistical analyses identified 33 proteins with consistent changes (≥2-fold) in RN181-transformed signaling plays a role in regulation of liver cirrhosis and hepatocellular carcinoma. The activation of oncogenes and the inactivation of tumor suppressor genes by mutations or chronic hepatitis virus infections play key roles in the pathogenesis of hepatocellular carcinoma (HCC). Here we report that RN181, a really interesting new gene finger domain-containing protein, was down-regulated in highly malignant cell lines and in tumor cells of 139 HCC clinical samples in comparison with adjacent normal liver tissues. The expression of RN181 was strongly associated with the pathological grade of HCC. Alterations of the expression of RN181 by retrovirus-transduced upcells. Ten of these proteins were up-regulated by RN181, and 23 were down-regulated. Representative proteins were validated by western blotting. Interaction network investigations revealed that 20 RN181-regulated proteins could integrate several key biological processes such as survival, metabolism, and mitogen-activated protein kinase (MAPK) pathways. Remarkably, 11 of the 33 proteins are associated with MAPK signaling in one or more ways. RN181 suppressed the tyrosine and HCC clinical samples, and removing the suppression increased tumor growth. phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) in cell lines and in tumor cells of xenografts
associated with MAPK signaling in one or more ways. RN181 suppressed the tyrosine phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) in cell lines and in tumor cells of xenografts and HCC clinical samples, and removing the suppression increased tumor growthHepatocellular carcinoma (HCC) is one of the most common malignant tumors and the third-leading cause of death from cancer worldwide with 600,000 deaths per year.1 HCC has characteristics of rapid growth, early vascular invasion, and high resistance to standard chemotherapy. For early or localized disease, surgical resection or liver transplantation is a curative treatment. However, approximately 80% of HCC patients present with advanced disease that is not amenable to surgical resection or transplantation and thus have a poor prognosis.2 Recently, in a randomized phase III trial, sorafenib, a multikinase inhibitor with potent activity against v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), vascular endothelial growth factor receptor 2, vascular endothelial growth factor receptor 3, c-kit, and platelet-derived growth factor receptor α (among others),3 was shown to prolong the median survival time of HCC patients from 7.9 to 10.7 months.4 Significantly, this was the first time that a systemic therapy produced clinical benefits in patients with advanced HCC, and the results will facilitate the identification of novel targets for the development of targeted therapies.

HCC has a complicated molecular tumorigenesis in which two mechanisms may predominate.5 One is cirrhosis associated with hepatic regeneration after tissue damage caused by a chronic hepatitis B or C virus infection, chronic alcohol consumption, toxins, or metabolic influences.

Reference :

Chiung-Fang Chang is currently a Researcher at Far Eastern Memorial Hospital, Taiwan. She graduated from National Taiwan University. She has received her PhD Degree in the Division of Biological Sciences at University of California, USA.

The authors thank Dr. Shu-Hong Luo (University of Illinois, Urbana-Champaign, IL) for the gift of the pLNCX2 vecto

This work is partly presented at 15th Asia Pacific Oncologists Annual Meeting, September 5-6, 2018 Tokyo, Japan