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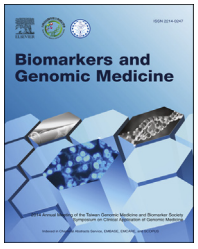

ABSTRACT

Autophagy regulates human hepatocellular carcinoma tumorigenesis through selective degeadation of cyclin D1

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Background: Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection induces progressive chronic liver diseases including hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC). HCC prognosis is poor because it is often diagnosed at late stages and incompletely understanding of virus-related HCC progression and the extent of marker variability among HCC patients. Therefore, development of new strategies that aim to reduce the risk of HCC in patients who are chronically HBV or HCV infected is an urgent demand.

Materials and Methods: HCC tissue arrays (147-paired specimens) were purchased from Taiwan Liver Cancer Network, Zhunan and National Cheng Kung University Hospital, Tainan, Taiwan. HBx transgenic mouse model and orthotopic liver tumorigenesis model in rat were utilized to clarify the relationship between cyclin D1 and autophagy in liver tumorigenesis. Autophagosomes were purified from liver cancer cells and immunogold-labeled antibody was used to detect cyclin D1 under the transmission electron microscopy.

Results: Autophagic activity was inversely correlated with cyclin D1 expression and high cyclin D1 expression accompanied with low autophagic activity correlated with poor overall survival rate in 147-paired HCC patients. Our animal studies showed that the off-label use drug amiodarone-induced autophagy suppressed liver tumor formation through degradation of cyclin D1 and inhibition of cell proliferation. Further study revealed that ubiquitinated cyclin D1 was selectively recruited into the autophagosome by binding with the receptor protein SQSTM1/p62, which is further degraded after fusion with lysosome. In summary, we are the first to reveal that autophagy regulates cell cycle process by selectively regulation of cyclin D1 through p62 mediated degradation pathway in HCC.

Discussion: Impaired autophagy in liver is a risk of HCC development, but the knowledge of signaling pathways that autophagy involved in the liver tumorigenesis is limited. Our *in vitro* and *in vivo* studies show that amiodarone-induced autophagy suppresses liver tumor formation through degradation of cyclin D1. Altogether, activation of autophagic activity suggests therapeutic opportunities for HCC and amiodarone is a potential anticancer agent against HCC tumorigenesis.

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