World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:10, No:10, 2016

Autophagy Regulates Human Hepatocellular Carcinoma Tumorigenesis through Selective Degradation of Cyclin D1

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Abstract : In hepatocelluar carcinoma (HCC), dysregulated expression of cyclin D1 and impaired autophagy has been reported separately. However, the relationship between them has not been explored. In this study, we demonstrated that autophagy was inversely correlated with cyclin D1 expression in 147 paired HCC patient specimens. HCC specimen with highly expression of cyclin D1 shows correlation with poor overall survival rate. Furthermore, induction of autophagy by amiodarone (antiarrhythmic drug) in Hep 3B cells, cyclin D1 was recruited into autophagosomes demonstrated by immune-gold labeling of cyclin D1 after extraction of autophagosomes. We further demonstrated that autophagy suppresses Hep 3B cell proliferation, and further analysis revealed that cell cycle was arrested at G1 phase. The interaction between LC3 (maker of autophagy) and cyclin D1 was increased after autophagy induction. In addition, ubiquitinated-cyclin D1 was also increased after autophagy induction, which is selectively degraded by autophagosome through binding with SQSTM1/p62 (an adaptor protein). In vivo study showed that amiodarone induced autophagy suppresses liver tumor formation in xenograft mouse and orthotopic rat model through decreasing cyclin D1 expression and inhibition of cell proliferation. Altogether, we reveal a novel mechanism that ubiquitinated cyclin D1 degraded by autophagic pathway by p62 and amiodarone is a promising drug for targeting cyclin D1 in liver cancer therapy.

Keywords : autophagy, cyclin D1, hepatocellular carcinoma, amiodarone
Conference Title : ICRACB 2016 : International Conference on Regulators of Autophagy and Cell Biology
Conference Location : Osaka, Japan
Conference Dates : October 10-11, 2016