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Distinct roles of α-1,2-mannosidase subtypes in Hepatocarcinogenesis: MAN1A1 is an oncogene and MAN1C1 is a tumor suppressor gene

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Deregulation of α-mannosidase can result in cancer, although the mechanism remains unclear. Here, we report the distinct roles of α-mannosidase subtypes in the formation of hepatocellular carcinoma (HCC). Clinicopathological analysis revealed that the clinical stage, tumor size, tumor type, α-fetoprotein level and invasion status were positively correlated with the expression level of *MAN1A1, MAN1B1*, and *MAN1A2*. In contrast, the expression of *MAN1C1* was decreased as early as stage I HCC. Survival analysis showed that high *MAN1A1*, *MAN1A2* or *MAN1B1* and low *MAN1C1* expression levels were significantly correlated with poor survival. Functionally, the overexpression of *MAN1A1* promoted proliferation, migration and transformation *in vitro* as well as metastasis in transgenic zebrafish. Conversely, the overexpression of *MAN1C1* reduced the cellular migration ability both *in vitro* and *in vivo*, decreased the colony formation ability, and shortened the S phase of the cell cycle. Furthermore, the expression of cell cycle/proliferation- and migration-related genes was increased in *MAN1A1*-overexpressing cells but decreased in *MAN1C1*-overexpressing cells. Finally, *MAN1A1* activated the expression of key regulators of the unfolded protein response (UPR) and the active spliced form of XBP1. Subsequently, treatment with an ER stress inhibitor decreased the expression of cell cycle/proliferation-related genes. Using a zebrafish model of liver-specific overexpression of *MAN1A1*, we observed steatosis and inflammation at earlier stages and HCC formation at a later stage. These data suggest that the up-regulation of *MAN1A1* activates the UPR and initiates metastasis. Thus, our data demonstrate that *MAN1A1* represents a novel oncogene in hepatocarcinogenesis, whereas *MAN1C1* acts as tumor suppressor gene.

Biography

Chiou-Hwa Yuh has completed her PhD from National Yang-Ming University in Taiwan, and Postdoctoral studies from California Institute of Technology in USA. She was famous in Developmental Gene Regulatory Networks. She initiated the systematic analysis of hepatocellular carcinoma (HCC) in mouse model, and established transgenic zebrafish model. She further developed the drug screening platform to identify novel small molecules which are effective in treatment HCC and lower toxicity compared to Sorafenib. She has published 41 papers in reputed journals and has been serving as an Editorial Board Member of repute journals.

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