Hydrogen peroxide inducible clone-5 mediates positive feedback ROS-JNK-c-jun signaling for HCC progression

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Abstract

The poor prognosis of hepatocellular carcinoma (HCC) is due to high recurrence rate mainly caused by intrahepatic metastasis. Hic-5 (hydrogen peroxide inducible clone-5) which belongs to the paxillin superfamily can be stimulated by a lot of metastatic factors including transforming growth factor (TGFβ) and hepatocyte growth factor (HGF), which further regulate epithelial mesenchymal transition (EMT), migration and invasion. The molecular mechanisms for Hic-5 to trigger EMT and tumor progression appeared to be closely associated with its impact on signal transduction. Our recent report demonstrated that Hic-5 not only can be a poor prognosis marker for HCC but also served as a mediator of the reactive oxygen species (ROS)-c-jun-N-terminal kinase (JNK) signaling pathway for HCC progression. Notably, Hic-5 appeared to locate both upstream and downstream of ROS-JNK cascade. In our recent study, a more comprehensive Hic-5-ROS-JNK positive feedback pathway has been established. Specifically, Hic-5 may interact with regulators of NADPH oxidase such as Rac-1, Traf4 and nonreceptor tyrosine kinase (Pyk2) for activating NADPH oxidase and ROS generation, leading to JNK phosphorylation and transcriptional activation of Hic-5 mediated by c-jun/AP-4. The Hic-5 thus induced in turn re-activates the ROS-JNK signal cascade. This positive feedback circuit is essential for elevating mesenchymal transcriptional factors such as Snail, Zeb1 and matrix degradation enzyme MMP9 and decreasing the epithelial marker E-cadherin (Fig.1). Currently, the missing links in both the upstream and downstream of Hic-5-NADPH oxidase-ROS-JNK-c-jun pathway are being clarified. Moreover, whether knockdown of Hic-5 in vivo may decrease HCC progression in a SCID mice are being investigated. Our study will benefit designing a more effective target therapy aiming at Hic-5 against HCC.

Speaker Biography:

Wen-Sheng Wu graduated from institute of biochemistry Taiwan University getting PhD degree on 1988. He carried postdoctoral research at department of research, veteran general hospital Taipei and department of Medical technology Kaohsiung, Taiwan. He is now a professor in Department of laboratory medicine and biotechnology, college of Medicine, Tzu Chi University. His research interest are. Signaling and transcriptional mechanisms for tumor progression and Target therapy against cancer.

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