

Submitter Name: Shuping Zhong
Submitted email: szhong@usc.edu

Alcohol-induced histone H3 phosphorylation modulates deregulation of Brf1 and tRNA genes in hepatocellular carcinoma

Mingen Lin^{1,3}, Zaifa Hong^{2,3}, Yanmei Zhang^{1,3}, Daniel Levy³, Shuping Zhong³

¹The First Affiliated Hospital, Shantou University Medical College; ²Affiliated Cancer Hospital and Institute of Guangzhou Medical University; ³Keck School of Medicine, University of Southern California.

Alcohol consumption enhances the risk of human cancer, more and more attentions are paid to this issue. Deregulation of Pol III genes, such as tRNAs and 5S rRNAs, tightly links to tumor development. Cancer causes chronic pain, which involves interactions and crosstalk between the cancer, the primary afferent nociceptor, and the immune system in DRG. Brf1 is a key transcription factor of tRNA genes. tRNAs are the precursors of non-coding small RNAs. Most of small RNAs are derived from cleaved tRNAs called as tRFs (tRNA-derived fragments), such as circRNA, miRNA, siRNA and so on. tRFs are abundant and have been implicated in opioid-mediated cancer pain. Alcohol-feeding promoted HCC of HCV NS5A transgenic mice. The transcription of Brf1 and tRNAs were dramatically increased in the tumor liver tissues, compared to non-tumor liver tissues. Alcohol enhanced the cellular levels of Brf1 and tRNA gene transcription in engineered HepG2-ADH cells. Alcohol strongly induces activation of MSK1 and H3ph (histone H3 phosphorylation) in liver cell lines. Study indicate that H3ph takes party in opioid-mediated pain relief. We have demonstrated that MSK1 mediates H3ph, inhibition of MSK1 by a chemical, SB 747651A, inhibits alcohol-induced H3ph. Blocking MSK1 signaling by the inhibitor significantly decreases Brf1 expression and tRNA gene transcription. This suggests that alterations of H3ph and tRFs may relieve cancer pain. Deepen studying the H3ph and tRFs may provide a possibility that establishing novel approach by inhibiting H3ph and tRFs may replace opioid analgesics to reduce the risk of addiction.