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GLYCINE/SARCOSINE RATIO AS NOVEL BIOMARKER FOR ALCOHOL-INDUCED LIVER FIBROSIS UNDER SUMOYLATION CONTROL

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Propose: Alcohol-induced liver fibrosis/disease (ALD) is characterized by excessive deposition of extracellular matrix (ECM) components in response to chronic abuse that could lead to cirrhosis and hepatocellular carcinoma development. Sarcosine is a derivative of the amino acid glycine, formed by the enzymes glycine N-methyl transferase (GNMT) or dimethylglycine dehydrogenase (DMGDH) and converted back into glycine via sarcosine dehydrogenase (SARDH). GNMT is silenced in human alcohol-induced cirrhosis. In addition, GNMT knockout mice develop oxidative stress, liver injury, fibrosis, and HCC. *SUMOylation* is a post-translational modification that requires an essential E2-conjugating enzyme 9 (UBC9) to covalently bind of small ubiquitin modifier (SUMO) and plays an important role in a wide range of cellular processes. We previously demonstrated that UBC9 level is induced in intragastric ethanol-infusion (EI) treated mouse liver. We performed SUMO-proteomics of alcohol-fed mouse liver and identified altered sumoylation of GNMT and SARDH. The goal of this work is to examine whether the dysregulated SUMOylation could regulate GNMT and SARDH enzymatic function in ethanol-induced liver fibrosis and elucidate the molecular mechanism(s).

Methods: Studies were performed using mouse hepatocytes (HEP), kupffer cells (KCs) and stellate cells (HSCs) from in vivo acute and chronic ethanol-fed mouse models and primary human HSCs. Oxidative stress and metabolic markers were measured using commercial kits.

Results: We found that ethanol treatment in vivo induced UBC9 expression in HSCs and HEP and inhibited its expression in KCs. This was associated with increased GNMT sumoylation and total levels, specifically in HSCs. In contrast, SARDH sumoylation fell in HSCs despite an increase in its total level. Ethanol feeding increased glycine and lowered sarcosine levels in mouse plasma, suggesting a potential regulation of GNMT/SARDH enzyme activity. Ethanol-treated co-culture model (HEP, HSCs and KCs) showed increase in ROS production in all liver cells and glycine/sarcosine ratio in HSCs but not in HEP and KCs compared to control. *Ubc9* silencing in HSCs inhibited ethanol-mediated ROS production and induction of HSC activation.

Conclusions: This data strongly suggests that oxidative stress-induced sumoylation plays a key role in HSC activation and this may influence the transmethylation machinery. Alterations of glycine/sarcosine ratio as a consequence of enzyme sumoylation could be considered as novel biomarker for ALD.

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