Alcohol-induced fatty liver is modulated by glycogen

With the support by the National Natural Science Foundation of China and the Ministry of Science and Technology of China, Prof. Chen Yan's (**陈雁**) laboratory at the Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, reported the function of glycogen in alcohol-induced fatty liver formation, which was published in the *Journal of Lipid Research* (2015, 56: 1329—1339).

Ethanol (EtOH), as a toxin to liver, may lead to fatty liver and various liver injures. EtOH itself is a macronutrient and 1 g of EtOH has seven calories, higher than carbohydrate and protein. Alcoholic liver disease is a major health problem worldwide and hepatic steatosis is an early response to alcohol consumption. Fat and glycogen are two major forms of energy storage in the liver; however, whether glycogen metabolism in the liver impacts alcohol-induced steatosis has been elusive. In this study, we used a mouse model with overexpression of PPP1R3G in the liver to dissect the potential role of glycogen in alcohol-induced fatty liver formation. PPP1R3G is a regulatory subunit of protein phosphatase 1 and stimulates glycogenesis in the liver. Chronic and binge EtOH feeding reduced the glycogen level in the mouse liver and such inhibitory effect of EtOH was reversed by PPP1R3G overexpression. In addition, PPP1R3G overexpression abrogated EtOH-induced elevation of serum levels of alanine aminotransferase and aspartate aminotransferase, increase in liver triglyceride concentration, and lipid deposition in the liver. EtOH-stimulated SREBP-1c was also reduced by PPP1R3G overexpression *in vivo*. In AML-12 mouse hepatocytes, PPP1R3G overexpression could relieve EtOH-induced lipid accumulation and SREBP-1c stimulation. In conclusion, this study indicates that glycogen metabolism is closely linked to EtOH-induced liver injury and fatty liver formation, thus unraveling a new perspective about a link between glycogen and triglyceride in alcoholic fatty liver formation.

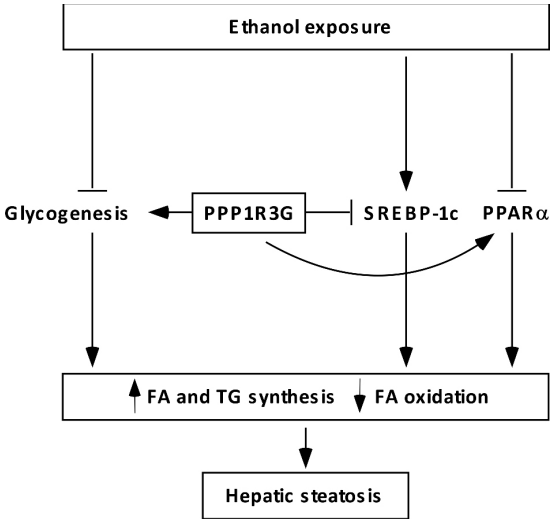

Figure Chronic alcohol exposure induces fatty liver formation through increased lipogenesis via stimulation of SREBP-1c and reduced fatty acid oxidation via inhibition of PPARα. Alcohol exposure reduces glycogenesis via inhibition of glycogen synthase (GS) activity, resulting in reduction of liver glycogen and release of free glucose that fuels lipogenesis. Increase of liver glycogen, such as via PPP1R3G overexpression, reduces glucose release and consequently reduces lipogenesis upon alcohol exposure. In addition, PPP1R3G overexpression could abrogate alcohol-mediated stimulation of SREBP-1c and inhibition of PPARα, contributing to reduction of hepatic steatosis.