SNX10 mediates alcohol-induced liver injury and steatosis by regulating the activation of chaperone-mediated autophagy

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Shen XiaoYan (沈晓燕) at the Department of Pharmacology, School of Pharmaceutical Sciences, Fudan University, recently reported that SNX10 is an important negative regulator of alcohol liver disease, which was published in *Journal of Hepatology* (2018, pii: S0168-8278(18)30118-1.).

Alcoholic liver disease is a major cause of morbidity and mortality worldwide. However, the cellular defense mechanisms underlying ALD are not well understood. Chaperone-mediated autophagy (CMA) is a type of autophagy for the degradation of cytosolic proteins with a specific pentapeptide motif. Growing evidence highlights the involvement of CMA in regulating hepatic lipid and carbohydrate metabolism and suggests that dysfunction of CMA may play a major role in hepatic metabolic dysregulation. Sorting nexin (SNX) 10 has been reported to possess a regulatory function in the endosomal/lysosomal pathway, which is required for CMA to execute its function. They therefore hypothesized that SNX10 might have a role in the pathogenesis of ALD by regulating CMA activity.

In the present study, they found that deficiency of SNX10 up-regulated CMA activity through inhibiting the maturation of Cathepsin A which is a key enzyme for LAMP-2A degradation. Further investigation showed that increased CMA activation inhibits proteasome activity, resulting in the activation of Nrf2-HO1 and AMPK signaling pathways, and thus preventing ethanol-induced hepatic injury and lipid metabolism disorder.

Their study reveals a crucial role for SNX10 in regulating CMA activity, and provides evidence for SNX10 as a potential promising therapeutic target for halting injury in ALD. They propose that SNX10 may be an attractive target for future therapeutic interventions aimed at enhancing CMA activity in ALD.

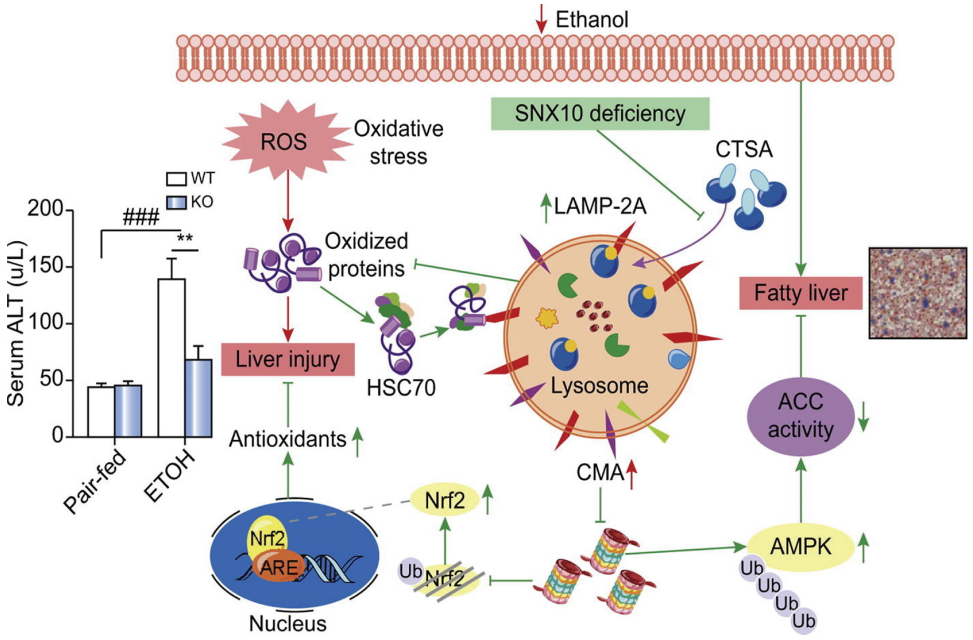

Figure Schematic representation of SNX10-regulated CMA in alcohol-induced liver injury and steatosis.