Down-regulation of *Cyp2e1*, *Cyp4al0* and *Cyp4a14* alleviates alcoholic liver injury by reducing oxidative stress

Authors
Qi Zhang[1], Shuang Wu[1], Cai Zhang[1] ,Qiubing Chen[2], Hao Yin[2], Yuan Wei[1,*]

Affiliations
1 School of Pharmacy, Jiangsu University, Zhenjiang 212013, China
2 Department of Urology, Frontier Science Centre for Immunology and Metabolism, Medical Research Institute, Zhongnan Hospital of Wuhan University, Wuhan University, Wuhan 430071, China

Abstract
Alcoholic liver disease (ALD) due to heavy drinking has become an increasingly concerning issue, but a specific medicine is currently lacking. The high consumption of alcohol and subsequent oxidative metabolism by cytochrome P450 (CYP) can produce a large number of reactive oxygen species to overwhelm cellular defenses and damage hepatocytes. With RNA interference-based inhibition of *Cyp2e1*, our previous studies have clarified the crucial role of CYP2E1 in the occurrence of ALD. Since there are some compensatory pathways such as CYP4A10 and CYP4A14, CYP2E1 is not sufficient to cover entire oxidative stress pathways *in vivo*, so we combined triple siRNAs lipid nanoparticles (LNPs) simultaneously targeting *Cyp2e1*, *Cyp4a10* and *Cyp4a14* genes to treat chronic ALD. In this study, triple siRNAs LNPs treated ALD model mice fed on Lieber-DeCarli ethanol liquid diet for 12 weeks at the early (1st week), middle (5th week) and late (9th week) stages. The results determined that the administration of triple siRNAs LNPs significantly ameliorated the chronic alcoholic liver injury of mice, and the early treatment achieved most obvious effects. It is probably owing to the reduction of oxidative stress and increase of antioxidant capacities by up-regulating *Gsh-Px*, *Gsh-Rd* and *Sod1*, the alleviation of inflammation by inhibiting the expression of *IL-1β*, *Il-6*, *Tnf-α* and *Tgf-β*, the prevention of excessive lipid synthesis by restoring the expression of *Srebp1c*, *Acc* and *Fas*, the maintaining of normal lipid oxidation metabolism by up-regulating *Cpt1* and *Pgc-1α*, and the suppression of ferroptosis by reversing the down-regulation of *GPX4*, *Nrf2* and *HO-1* induced by alcohol. In brief, our study innovatively developed the triple siRNAs LNPs targeting *Cyp2e1*, *Cyp4a10* and *Cyp4a14*, conceivably revealed the mechanism of oxidative stress in ALD, suggestively provided potential targets and intervention references of ALD clinical treatments.
Keywords: Alcoholic liver disease ; lipid nanoparticles ; siRNA ; oxidative stress ; *Cyp2e1* gene