Role of genetic HSD17B13 variation in experimental alcoholic liver fibrosis

Summary

Background: Alcoholic liver disease (ALD) accounts for over fifty percent of all chronic liver diseases in industrialized countries and is responsible for >40,000 deaths in 2005 in Europe alone. Progression of ALD is highly variable with only 20% of heavy drinker developing cirrhosis, and modulated by environmental factors such as gender, obesity and coinfection with chronic viral hepatitis. The global quest for genetic factors that modulate the progression of ALD has identified a genetic variant in patatin-like phospholipase domain containing 3 (PNPLA3 rs738409 G>C) as the strongest single genetic risk locus for progressive alcoholic liver injury by means of candidate gene and genome-wide case control studies. Recently, a splice variant (rs72613567:TA) in HSD17B13, encoding the hepatic lipid droplet protein hydroxysteroid 17-beta dehydrogenase 13 has been identified by exome-wide scanning as the first protective genetic factor towards alcoholic and non-alcoholic fatty liver disease.

Aims: With the current research we intend to model the impact of genetic HSD17B13 variation on the progression of ALD using mice which carry either a hsd17b13 point mutation inserted by CRISPR/Cas9 technology or are wild type for the respective gene locus.

Methods: Mice will be subjected to chronic alcohol administration, and biochemical, histological and molecular liver read-outs will be determined. Specifically, serum liver enzymes, standard histology, immunohistochemistry, surrogate markers of fibrosis, steatosis and inflammation, and morphometry will be assessed and compared between groups.

Expected value: The proposed study has the potential to enhance our understanding of the role of the first putative protective genetic locus in ALD. Confirming the modulating effect of HSD17B13 rs72613567:TA in experimental ALD would contribute to answering the question why some drinkers develop ALD, and others do not when exposed to equal amounts of alcohol. The gained insight would foster the development of preventive strategies based on gene signatures, and hopefully, novel treatments.