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Zhuoyao Lyu

University of Massachusetts Medical School

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HEPATIC CHANGES ASSOCIATED WITH CHRONIC ALCOHOL EXPOSURE IN AN ALPHA-1 ANTITRYPSIN PIZ MOUSE MODEL

Zhuoyao Lyu¹, Alisha M. Gruntman DVM, PhD^{1,2,4}, Brian O'Sullivan-Murphy MD, PhD³, Christian Mueller PhD^{1,4}, Terence R Flotte MD^{1,4}

¹Horae Gene Therapy Center, University of Massachusetts Medical School; ²Department of Clinical Sciences, Tufts Cummings School of Veterinary Medicine; ³Lovelace Respiratory Research Institute; ⁴Department of Pediatrics, University of Massachusetts Medical School

The PiZ mutation in the alpha-1 antitrypsin (AAT) gene causes the PiZ mutant protein to be sequestered in the endoplasmic reticulum of hepatocytes, causing significant liver pathology in ~10% of PiZZ homozygous AAT disease patients. Current transgenic mouse models of the disease include the liver-specific over-expression of mutant PiZ protein. However, these animal models do not efficiently recapitulate the liver damage found in PiZZ homozygous patients. Since only a small percentage of patients develop liver disease and it is not reproducible in animal models of AATD, it suggests that there are other factors that participate in disease pathogenesis. Here, we propose that in the presence of alcohol, liver injury will be initiated and that the intensity of the disease will be exacerbated by the presence of accumulated PiZ mutant protein. To test this hypothesis, we have administered alcohol via the Lieber-DeCarli diet regimen to PiZ transgenic and control C57Bl/6 mice for 12 weeks. We found no difference in alcohol and non-alcohol fed mice in terms of elevations in liver enzymes (AST and ALT). We did find a difference in the degree of steatosis and inflammation in the livers of alcohol fed PiZ mice over those of control alcohol fed mice. These findings are consistent with a chronic low-level hepatic insult seen in chronic alcohol consumption. The difference between PiZ and control mice will allow us to test gene therapies that prevent the accumulation of PiZ aggregates within hepatocytes to determine if they will prevent the exacerbation of alcoholic liver disease.

Contact:

Alisha Gruntman

University of Massachusetts Medical School

Alisha.Gruntman@umassmed.edu