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Role of miR-122 in Acetaminophen Induced Liver Injury

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ABSTRACT

Acetaminophen (APAP) toxicity is a major cause for acute liver failure (ALF). Although circulating miR-122 is a sensitive biomarker of ALF, role of this most abundant liver specific miRNA in ALF has not been elucidated. Here, we show that miR-122 is downregulated in liver biopsies of ALF patients compared to non-ALF biopsies and in the livers of mice treated with APAP. A dramatic decrease in the primary-miR-122 expression occurs upon APAP overdose in mice due to suppression of its two key trans-activators, HNF4α and HNF6. More importantly, the mortality rates of both male and female liver-specific miR-122 knockout (LKO) (Mir122loxP/loxP; Alb-Cre) mice were significantly higher than that of the age- and sex-matched control (Mir122loxP/loxP) mice when injected intraperitoneally with a dose of APAP lethal to LKO mice. Higher basal levels of CYP2E1 and CYP1A2 that convert APAP to highly reactive N-acetyl-p-benzoquinone imine (NAPQI) are contributing factors to the sensitivity of LKO mice to APAP overdose. Upregulation of Cyp1a2 primary transcript and mRNA in LKO livers correlated with elevation of Ahr and Med1, two trans-activators of Cyp1a2 gene. Analysis of ChIP-seq data in the ENCODE database identified association of CTCF with Ahr promoter in mouse livers. Both MED1 and CTCF are validated conserved miR-122 targets. Furthermore, depletion of Ahr, Med1 or Ctcf in Mir122-/− hepatocytes reduced Cyp1a2 expression. Glycerol density gradient centrifugation and pulse-chase studies showed that Cyp2e1 is upregulated in LKO hepatocytes at the protein level. Notably, miR-122 depletion sensitized differentiated human HepaRG cells to APAP toxicity that correlated with upregulation of AHR, MED1 and CYP1A2 expression. Collectively, these results suggest a critical role of miR-122 in acetaminophen detoxification and implicate its therapeutic potential in ALF.
RECENT ABSTRACTS AND PRESENTATION


2014: Presentation entitled “Role of microRNA-122 in Drug Induced Liver Injury” in Research in Progress seminar series in Experimental Pathology seminar program in the Pathology Department, The Ohio State University
2013: Presentation entitled “Role of MicroRNA-122 in Drug Induced Liver Injury” in Research in Progress Seminar, Department of Molecular and Cellular Biochemistry, The Ohio State University.
Vivek Chowdhary, Kun-yu Teng, Sharda Thakral, et al. miR-122 protects mice and human hepatocytes from acetaminophen toxicity by regulating CYP1A2 and CYP2E1 expression. Submitted for review
AWARDS AND HONORS

2015: Student Research Award, AASLD
2015: Travel Award, RC-SIRM Symposium and Workshop, UKY

FUTURE PLANS

Following graduation, I am planning to continue my research in liver toxicity as a post-doctoral fellow and after that, I will pursue a position as liver toxicity researcher in academia. Ultimately, I would like to work towards development of novel drugs with wider therapeutic index.