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**Topic Category:** 4069-ASIP LIVER PATHOBIOLOGY**First Author:** Chao XuDepartment of Physiology & Neurobiology, University of Connecticut 75N. Eagleville Rd. Storrs, CT 06269  
United States**Phone:**

chao.2.xu@uconn.edu

**First Author is a:** Postdoctoral Fellow**First Author is a member of:** American Society for Investigative Pathology**First Author Degree:****Presentation Preference:** Oral**Sponsor:** Li Wang**Sponsor Phone:** 8606175344

li.wang@uconn.edu

**Sponsor's Society:** Pathology - American Society for Investigative Pathology (ASIP) - Host Society**Keywords:** 1. acute liver injury 2. Acetaminophen 3. autophagy**Awards:** ASIP Trainee Travel Award, ASIP Promoting Diversity in Science Trainee Travel Award, HCS-Sponsored Trainee Travel Award**Hepatocyte Specific Knockout of microRNA-21-5p Alleviates Acetaminophen-Induced Hepatotoxicity by Activation of Autophagy**

Chao Xu, Li Wang. Department of Physiology &amp; Neurobiology, University of Connecticut, Storrs, CT

**Background:** Acetaminophen (APAP)-induced liver injury is the most frequent cause of acute liver failure in the US and many other countries, constituting a significant threat to patient health and has an enormous economic impact on health care expenditures. Significant increase in the level of microRNA-21 in both liver tissues and in plasma have been observed in APAP overdosed animals and human. However, the mechanistic effect of miRNA-21 on acute liver injury remains unknown.

**Methods:** Wild-type and hepatocyte-specific miRNA-21 knockout (miR-21 HKO) mice were treated with a toxic dose of APAP (400 mg/kg i.p.) after fasting for 15 hr. Blood samples and liver tissues were collected at 2 hr and 12 hr after APAP treatment. Histopathological changes, serum ALT, AST, and GST levels were evaluated. The expression levels of proteins and genes involved in inflammation, necrosis, apoptosis, and autophagy were measured.

**Results:** miR-21 HKO mice were protected from APAP-induced hepatotoxicity. Noticeably, the increased survival and a reduction of necrotic hepatocytes were observed in miR-21 HKO mice after APAP treatment for 12 h. Compared with control littermates, miR-21 HKO mice showed significantly lower levels of ALT and AST, which was accompanied by the reduced mRNA levels of IL-1 $\beta$ , IL-6, TNF $\alpha$ , and iNOS in the liver. JNK activation plays a pivotal role in APAP-induced liver injury. However, the expression of phospho-JNK showed no significant difference between WT and miR-21 HKO mice. Both GSK3 $\beta$ -mediated early phase attack and ASK1-mediated late phase attack resulted in JNK activation. Consistently, there were no significant changes in these two pathways between WT and miR-21 HKO mice upon APAP treatment. Moreover, the expression of genes related to necrosis and apoptosis didn't change either. Interestingly, the expression of p62, LC-3B, and Beclin-1 was markedly induced in miR-21 ablated HKO compared to WT mice after APAP treatment, indicative of autophagy activation. Induction of autophagy can inhibit APAP-induced hepatotoxicity. AMPK and mTORC1 are two key sensors to control autophagy. Compared with control littermates, miR-21 HKO mice showed significantly higher level of AMPK after APAP treatment, which promoted the activation of autophagy. Interestingly, mTORC1 was also induced by miRNA-21-Deficiency.

**Conclusions:** Hepatocyte specific knockout of microRNA-21-5p alleviated APAP-induced hepatotoxicity by activation of autophagy. Our findings provide novel mechanism insights into the understanding of APAP-induced liver injury by miRNA-21.

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