

7471**Topic Category:** 4073-ASIP Liver injury and inflammation

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First Author is a: Graduate Student
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Presentation Preference: Oral

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Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society**Keywords:** 1. Probiotics 2. Oxidative Injury**Awards:** ASIP Trainee Travel Award

Regulation of oxidative liver injury by the probiotic *Lactobacillus rhamnosus* GG

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The gut microbiome is composed of a diverse and dynamic community of microorganisms colonizing the intestinal lumen and mucosa. Using germ-free model organisms, recent research has established the importance of these communities in influencing key metabolic, endocrine, and immunologic processes in the host. The majority of this research has focused on its effects on the intestine, the tissue with which the microbiome is in the most intimate contact. Recent studies, however, have revealed that these physiologic effects are significantly more far-reaching, with roles in hepatic, cardiovascular, and even neurological health. As the primary metabolic and detoxification hub, the liver is a critical checkpoint between the digestive functions of the gut and the rest of the body. Therefore, it is likely that liver health and homeostasis may be affected through alterations in the gut microbiota. This possibility presents an opportunity for therapeutic intervention in hepatic disease by modulating the bacterial communities in the lumen of the intestine. This can be accomplished through the oral administration of probiotics, a group of beneficial bacteria that can influence the health of the host. Previous work by our group demonstrated a key role for the widely-studied probiotic *Lactobacillus rhamnosus* GG (LGG) in protection against oxidative liver injury to the intestinal epithelium. It accomplishes this through activation of Nrf2, a basic leucine zipper transcription factor and master regulator of cellular antioxidant and xenobiotic responses. Here, we extend these findings by investigating the ability of LGG to augment this pathway in the liver. We performed daily administration of LGG by oral gavage to conventional mice. In these mice we observe increased hepatic Nrf2 activity relative to vehicle control as determined by increased Nrf2 stabilization, nuclear localization, and target transcription. Induction of the Nrf2 pathway has been shown to protect the liver from xenobiotic and oxidative stress. Indeed, LGG fed animals were protected against a challenge with acetaminophen, a potent inducer of hepatic oxidative stress. These data provide important mechanistic insights into the role of the microbiome and probiotics in regulating systemic host homeostasis.

Support or Funding Information

NIH RO1AI64462