The Role of Endogenous Antioxidant Pathways in Murine Non-alcoholic Steatohepatitis

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Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic steatohepatitis. The etiology of NASH is currently unknown, but data suggest the collagen accumulation and eventual fibrosis are a result of a reduced ability to clear reactive oxygen species (ROS) from the liver. Based on the molecular mechanisms and known function of the glutathione pathway in the removal of ROS, we hypothesized that a malfunction or overload of this pathway could contribute to NASH. We report that in our murine model of NASH, mice treated with high-fat-high-carbohydrate (HFHC) diets, or HFHC diets plus acetaminophen showed increased gene expression of the genes associated with the glutathione pathway, as well as reduced levels of GSH in the liver and plasma as compared to chow. They also showed an increased level of liver ROS as indicated by DHE stain. This suggests that while the mechanisms associated with the glutathione pathway are upregulated in NASH, the response is insufficient to clear the increased levels of ROS in the liver. This suggests a possible therapeutic strategy in the use of antioxidants or other treatments known to modulate and increase the activity of the glutathione pathway.