Introduction

Non-Alcoholic Steatohepatitis (NASH) affects ~25-30% of the US population, with 10-20% progressing to more severe disorders such as fibrosis, cirrhosis or hepatocellular carcinoma. The mechanism underlying the progression of fatty liver disease is unclear, however the gut-liver axis plays a key role in liver homestasis and may contribute. High mobility group box-1 (HMGB1) is a damage associated molecular pattern involved in numerous liver disorders, where it is released from damaged hepatocytes and activated immune cells. Furthermore, it is secreted from intestinal epithelial cells (IEC) during local injury where it contributes to gut inflammation. However, the role of HMGB1 in NASH has yet to be investigated in detail.

We hypothesized that HMGB1 from IEC may be involved in the onset and progression of NASH.

Our aim was to determine the role of gut derived HMGB1 in the pathogenesis of diet-induced NASH.

Methods

We used mice with conditional Hmgb1 ablation in IEC (Hmgb1flox/−) and Ctrl littermates as controls. Mice were fed a high-fat, high-cholesterol and high-fructose (HFCF) diet or an equicaloic control diet for 1 or 24 wk. The liver scoring system for NASH was used.

Results

Figure 2. Hmgb1flox/− mice display lipid accumulation in IEC after only 1 wk on HFCF diet. WT or Hmgb1flox/− mice fed HFCF or control diet for 1 wk. Liver H&E and Oil Red O stain (left), western blot of p-JNK (right). Hmgb1flox/− mice in IEC show increased p-JNK and increased cholesterol content of IEC compared to Hmgb1flox/− mice (C). Data are expressed as mean ± SEM (n=6).

Figure 3. Hmgb1flox/− mice are protected from hepatic steatosis after 1 wk on HFCF diet. WT and Hmgb1flox/− mice had HFCF or control diet for 1 wk. Liver H&E and Oil Red O stain (left), western blot of p-JNK and p-JNK:JNK (right). Hmgb1flox/− mice show decreased steatosis and inflammation in Hmgb1flox/− mice. Body weight change and liver to body weight ratio (C) did not increase in Hmgb1flox/− mice. ALT and AST activities were not significantly changed (D). Serum and liver triglycerides were decreased (E). Data are expressed as mean ± SEM (n=6).

Conclusions

We identified a novel role of HMGB1 in lipid accumulation in the gut in the early stages of NASH. Hmgb1flox/− mice fed HFCF diet show accumulation of lipids in the IEC of the jejunum, increased serum triglycerides and protection from hepatic steatosis after 24 wk. This suggests that HMGB1 plays a critical role in early stage gut damage and, by packaging the amount of fat transformed from the intestine to the liver and subsequent hepatic steatosis. HmGB1 may well serve as a target to treat lipid storage disorders and NASH.

References

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Further information on relevant topics and methodology can be found in various scientific publications and reviews related to non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and the role of HMGB1 in liver disease. These studies provide insight into the multifactorial nature of NASH and the potential therapeutic targets, such as HMGB1, to combat the disease. Continued research is essential to uncovering the mechanisms behind NASH and identifying effective treatments.