A Common Dietary Component Wheat Amylase Trypsin Inhibitors as Drivers of Chronic Liver Disease in Pre-Clinical Models of NASH and Liver Fibrosis

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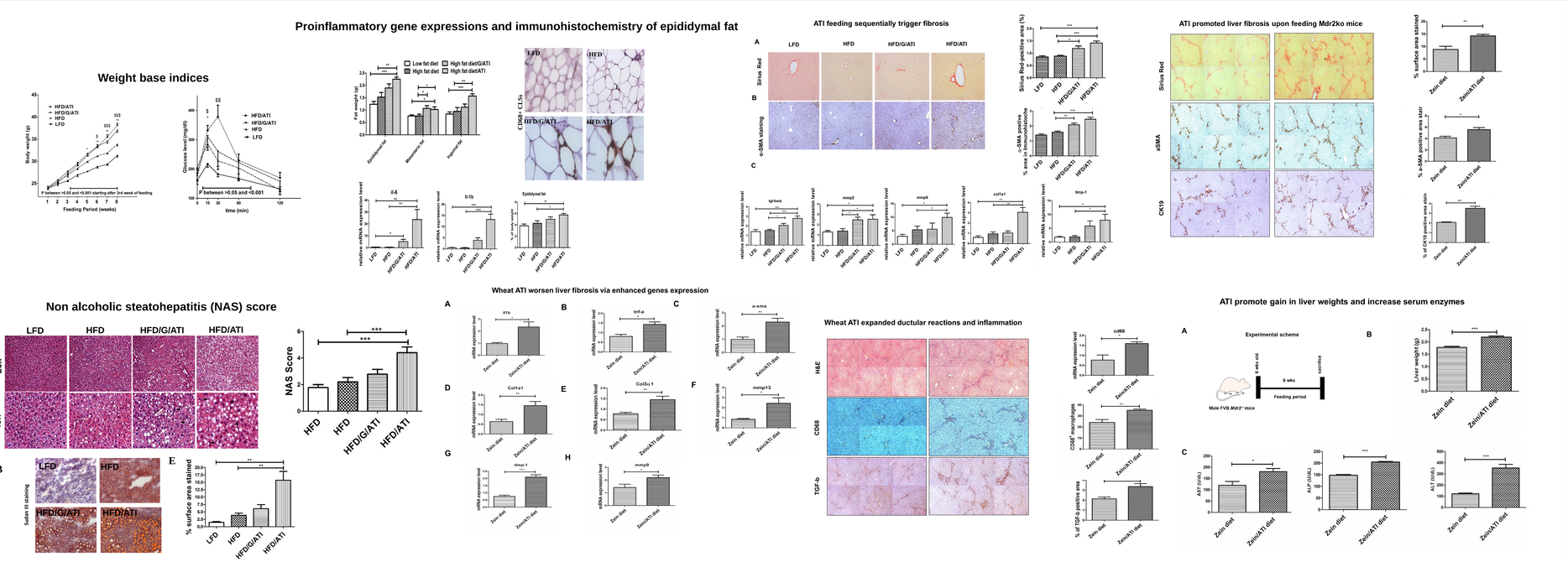
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BACKGROUND & AIMS

The gut-liver-axis has emerged an important driver of chronic liver disease. In line with this, specific food derived (non-tolerable) immunogenic signals from the gut are potentially the important contributors in worsening obesity and non-alcoholic fatty liver disease (NAFLD) and liver fibrosis. A common immunogenic component in food staple (that resist to intestinal degradation) are wheat amylase trypsin inhibitors (ATI) that activate intestinal macrophages and dendritic cells via toll like receptor-4 migrate and propagate the inflammatory stimulus to the peripheral organs such as liver. We therefore studied how far nutritional ATI would affect NAFLD and liver fibrosis in preclinical models of NASH and liver fibrosis.

METHOD

Male C57BI/6J mice received a carbohydrate and protein (zein) defined low fat or high fat diet (HFD), with or without 30% of the protein being replaced by wheat gluten (G, naturally containing 0.15g ATI per 10g), or 0.7% of the zein as purified ATI for 8 weeks. Male Mdr2-/- FVB mice were fed ATI containing and ATI free diets for 6 weeks. In the NASH model, insulin resistance (IR) was assessed by an intraperitoneal glucose tolerance test.



RESULTS

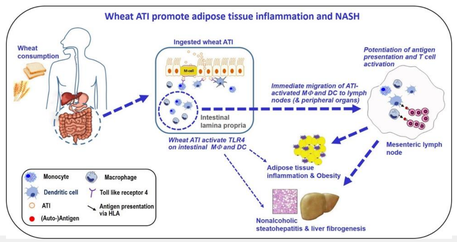
In NASH, mice on the HFD gained significant weight and developed IR. Compared to the HFD alone, mice fed the HFD/G/ATI or the HFD/ATI diets gained significantly more weight and displayed significantly higher serum transaminases and triglycerides, increased liver, epididymal, mesenteric and inguinal fat, and a higher insulin resistance. ATI feeding promoted liver and adipose tissue inflammation, M1 macrophage polarization and infiltration, and enhanced the fibrogenic response in the liver.

Moreover, there were significant increase in number of CD68+ macrophages, CD86+ dendritic cells and MHC-II+ cells in the distal part of the intestine of HFD/ATI diet compare to HFD diet alone. In the liver fibrosis model, Mdr2-/- FVB mice, liver transaminases and liver weights in the ATI fed group was significantly increased compared to the ATI free group.

Overall, liver transcripts for il1b, tnf-a, cd68, col1a1, a-sma and col3a1, mmp13, timp1 and mmp9 were significantly upregulated in the ATI fed vs ATI-free groups. Moreover, ATI feeding has increased ductular reactions (revealed by H&E) and hepatic macrophage infiltration (CD68 immunohistochemistry) in Mdr2-/- FVB mice vs ATI free diet. Moreover, ATI feeding accelerated fibrosis progression evident by a higher collagen deposition in the ATI-fed mice showed by Sirius red morphometry and Alpha-SMA immunohistochemistry.

CONCLUSIONS

When ingested in quantities comparable to average human consumption, wheat ATI exacerbate the key features of rodent NAFLD and the metabolic syndrome despite their irrelevant caloric value. Moreover, dietary ATI promoted liver fibrosis in the NASH and the Mdr2KO mouse model of PSC. ATI mediated NASH and liver fibrosis is outlined in Fig.1.



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