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Galectin-3 Ablation Enhances Liver Steatosis, but Attenuates Inflammation and IL-33-Dependent Fibrosis in Obesogenic Mouse Model of Nonalcoholic Steatohepatitis

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The importance of Galectin-3 (Gal-3) in obesity-associated liver pathology is incompletely defined. To dissect the role of Gal-3 in fibrotic nonalcoholic steatohepatitis (NASH), Gal-3-deficient (LGALS3$^{-/-}$) and wild-type (LGALS3$^{+/+}$) C57Bl/6 mice were placed on an obesogenic high fat diet (HFD, 60% kcal fat) or standard chow diet for 12 and 24 wks. Compared to WT mice, HFD-fed LGALS3$^{-/-}$ mice developed, in addition to increased visceral adiposity and diabetes, marked liver steatosis, which was accompanied with higher expression of hepatic *PPAR-γ*, *Cd36*, *Abca-1* and *FAS*. However, as opposed to LGALS3$^{-/-}$ mice, hepatocellular damage, inflammation and fibrosis were more extensive in WT mice which had an elevated number of mature myeloid dendritic cells, proinflammatory CD11b^{+}Ly6C^{hi} monocytes/macrophages in liver, peripheral blood and bone marrow, and increased hepatic *CCL2, F4/80, CD11c, TLR4, CD14, NLRP3* inflammasome, *IL-1β* and *NADPH*-oxidase enzymes mRNA expression. Thus, obesity-driven greater steatosis was uncoupled with attenuated fibrotic NASH in Gal-3-deficient mice. HFD-fed WT mice had a higher number of hepatocytes that strongly expressed IL-33 and hepatic CD11b^{+}IL-13^{+} cells, increased levels of IL-33 and IL-13 and upregulated *IL-33, ST2* and *IL-13* mRNA in liver compared with LGALS3$^{-/-}$ mice. IL-33 failed to induce ST2 upregulation and IL-13 production by LGALS3$^{-/-}$ peritoneal macrophages *in vitro*. Administration of IL-33 *in vivo* enhanced liver fibrosis in HFD-fed mice in both genotypes, albeit to a significantly lower extent in LGALS3$^{-/-}$ mice, which was associated with less numerous hepatic IL-13-expressing CD11b^{+} cells. The present study provides evidence of a novel role for Gal-3 in regulating IL-33-dependent liver fibrosis.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), which encompasses simple steatosis, nonalcoholic steatohepatitis (NASH), cirrhosis and possibly liver carcinoma, is strongly associated with obesity and metabolic syndrome and patients with type 2 diabetes are predisposed to develop a more severe form of fibrotic NASH (1,2). During obesity, immune cells infiltrated in visceral adipose tissue mediate chronic low-grade inflammation that plays a key role in the pathogenesis of NAFLD (1,3). In the progression from steatosis to NASH, fat deposition renders hepatocytes susceptible to inflammatory, lipid and oxidative stress mediators through as yet incompletely defined molecular mechanisms, resulting in liver inflammation and damage (3). In NASH, through secreted chemokines and cytokines, intrahepatic innate and adaptive immune cells sustain chronic inflammation and induce transdifferentiation of hepatic stellate cells (HSCs) into myofibroblasts, key cells in liver fibrosis (4).

Galectin-3 (Gal-3), the unique "chimera-type" β-galactoside-binding lectin, exerts both pro- and antiinflammatory roles, depending on disease condition. There is plethora of evidence of its proinflammatory role in immune-mediated inflammation (5–7) and organ-specific autoimmunity (8). However, Gal-3 attenuates macrophage sensitivity to endotoxin (9) and has a protective role in the setting of high-fat diet-induced obesity, adipose tissue inflammation, diabetes and atherosclerosis, partly by its ability to scavenge advanced glycation end products (AGE) and downregulate receptor for AGE (RAGE), thus preventing the consequent RAGE-dependent inflammation (10–12). Obese Gal-3-deficient mice had enhanced activation of NLRP3 inflammasome and NFκB in

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