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GALECTIN-3 DEFICIENCY EXACERBATES LIVER STEATOSIS BUT PROTECTS FROM STEATOHEPATITIS AND IL-33/IL-13 DEPENDENT FIBROSIS IN HFD-INDUCED OBESITY MOUSE MODEL

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Introduction: Gal-3 participates in the pathogenesis of metabolic disorders, but its importance in obesity-associated liver pathology is incompletely defined.
Aims: In this study, we aimed to dissect the role of Gal-3 in liver inflammatory response and fibrosis, key events in the pathogenesis and progression of nonalcoholic steatohepatitis (NASH) induced by obesogenic high-fat diet (HFD).

Material and Methods: Gal-3-deficient ($LGALS3^{-/-}$) and wild-type ($LGALS3^{+/+}$) C57Bl/6 mice received HFD (60% kcal fat) or standard chow diet for 24 weeks and metabolic parameters, gene expression and immunophenotypic analyses were performed.

Results: Compared to WT mice, HFD-fed $LGALS3^{-/-}$ mice developed, in addition to increased obesity and type 2 diabetes, more pronounced liver steatosis accompanied with increased hepatic PPAR-γ and Cd36 expression. However, ALT and AST levels, liver injury, inflammation and fibrosis scores, and hepatic procollagen and α-SMA mRNA expression were significantly lower in obese $LGALS3^{-/-}$ mice. In addition, livers of obese $LGALS3^{-/-}$ mice contained lower proportions of mature myeloid DCs, proinflammatory monocytes ($CD11b^{+}Ly6C^{hi}$) and M1-macrophages ($F4/80^{+}CD11c^{+}CD206^{-}$) and lower CCL2 chemokine, NLRP3 inflammasome and IL-1β mRNA expression compared to diet-matched WT mice. Furthermore, profibrogenic IL-33 and IL-13 in liver homogenates and hepatic IL-33, IL-33 receptor (IL-33R) and IL-13 mRNA expression were lower in $LGALS3^{-/-}$ mice than in WT mice, while hepatic TGF-β levels were similar. Moreover, in contrast to WT macrophages, $LGALS3^{-/-}$ peritoneal macrophages failed to upregulate IL-33R expression and IL-13 production *in vitro* in response to stimulation with recombinant mouse IL-33.

Conclusions: Gal-3 ablation promotes steatosis, but prevents liver injury, inflammation and fibrosis in obesogenic model of NASH by attenuating recruitment of proinflammatory myeloid cells and profibrogenic IL-33 and IL-13 in liver.