GPBAR1FUNCTIONS AS GATEKEEPER FOR LIVER NKT CELLS AND PROVIDES COUNTERREGULATORY SIGNALS IN AUTOIMMUNE HEPATITIS

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Background & Aims: GPBAR1, also known as TGR5, is a G protein–coupled receptor activated by bile acids. In the human body, the expression of GPBAR1is essentially restricted to the small intestine, gallbladder, adipose tissues, and cells of immune system. Hepatic innate immune cells are involved in the immunopathogenesis of human liver diseases and in several murine hepatitis models. Here, by using genetic and pharmacological approaches, we provide evidence that GPBAR1ligation attenuates the inflammation in rodent models of hepatitis.

Material and methods: Hepatitis was induced by concanavalin A (ConA) or α-galactosyl-ceramide (αGalCer). 6b-Ethyl-3a,7b-dihydroxy-5b-cholan-24-ol (BAR501), a selective agonist of GPBAR1, was administrated by o.s..

Results: In the mouse models of hepatitis, the genetic ablation of Gpabar1worsened the severity of liver injury and resulted in a type I NKT cells phenotype that was essentially biased toward a NKT1, a proinflammatory, IFN-γ producing, NKT cells subtype. In contrast, GPBAR1agonism rescued wild type mice from acute liver damage and redirects the NKT cells polarization toward a NKT10, a regulatory, IL-10 secreting, type I NKT cell subset. In addition, GPBAR1agonism significantly expanded the subset of Il-10 secreting type II NKT cells. RNAseq analysis of both NKT cells type confirmed that IL-10 is a major target for GPABR1. Accordingly, IL-10 gene ablation abrogated protection afforded by GPBAR1agonism in the ConA model.

Conclusions: Present results illustrate a role for GPBAR1in regulating liver NKT ecology. Because NKT cells are an essential component of liver immune system, our data provide a compelling evidence for a GPBAR1-IL-10 axis in regulating of liver immunity.