Liver defender macrophages: A novel discovery with therapeutic potential

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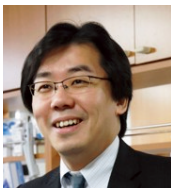

Abstract

Our research group has established an original platform that integrates advanced intravital imaging with spatially resolved single-cell transcriptomic analysis. Using this approach, we identified a distinct subset of macrophages localized around the hepatic portal entry that plays a critical role in protecting the liver from gut-derived exogenous substances. Furthermore, we demonstrated that these macrophages suppress the development of intractable liver diseases such as primary sclerosing cholangitis and metabolic dysfunction-associated steatohepatitis. In addition, we discovered that isoallo-lithocholic acid produced by specific longevity-associated gut microbiota is involved in the induction of these macrophages, highlighting its potential as a therapeutic lead compound.

Background & Results

The liver is directly connected to the gut through the portal vein, which enables efficient transport of dietary nutrients but also exposes the liver to gut-derived microorganisms and their products. Under physiological conditions, the liver prevents inflammation by rapidly neutralizing these exogenous components; however, the cellular basis and spatial regulation of this immunological defense have remained unclear.

To address this, we established an intravital liver imaging platform to visualize immune cell behavior in real time. We observed that inflammatory responses were selectively suppressed near the portal vein. To identify the responsible cells, we developed a regional cell isolation method and performed single-cell transcriptomic analysis, which identified a macrophage subset highly expressing the scavenger receptor Marco and the anti-inflammatory cytokine IL-10. This “immunoregulatory” macrophage population was enriched near the portal entry. Using mice deficient in Marco and IL-10, we demonstrated that loss of these molecules resulted in excessive inflammatory cell infiltration and aggravated liver injury following the exposure of exogenous substances. Furthermore, analysis of liver specimens from patients with primary sclerosing cholangitis and metabolic dysfunction–associated steatohepatitis revealed a significant reduction of this macrophage population. Consistent with these findings, animal models revealed that mice deficient in this macrophage function were more susceptible to accelerated steatohepatitis, cholangitis, and liver fibrosis.

We further discovered that the abundance of the immunoregulatory macrophages varied by animal facility and correlated with the presence of Odoribacteraceae, a bacterial family producing isoallo-lithocholic acid. Oral administration of isoallo-lithocholic acid increased Marco and IL-10 expression in hepatic macrophages, indicating its role in inducing the protective phenotype.

Significance of the research and Future perspective

This study elucidates a previously unrecognized hepatic immune system that protects both the liver and the host from gut-derived pathogens/antigens that continuously enter from the gut. Recent findings suggest that the gut-derived substances, when disseminated systemically, may contribute to the development of a wide spectrum of disorders, including diabetes, rheumatoid arthritis, asthma, and Alzheimer’s disease in addition to liver diseases. Based on our findings, therapeutic strategies that enhance the phagocytic and immunoregulatory capacity of hepatic macrophages using isoallo-lithocholic acid hold promise for preventing such diseases. Furthermore, targeted delivery of isoallo-lithocholic acid to macrophages in specific organs may enable the expansion of this approach to a broad range of inflammatory disorders across multiple tissues.

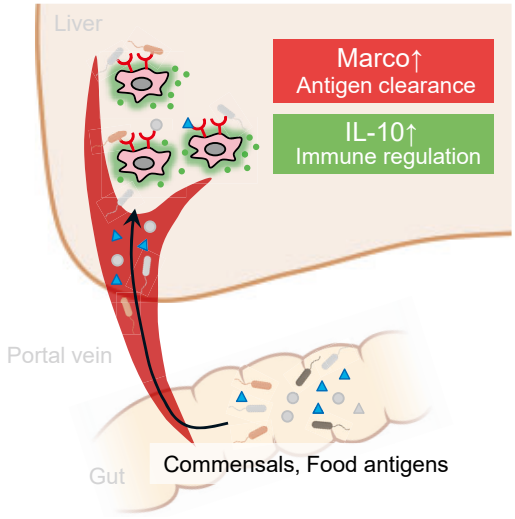

Fig. 1 Mechanisms of liver homeostasis maintenance by periportal macrophages

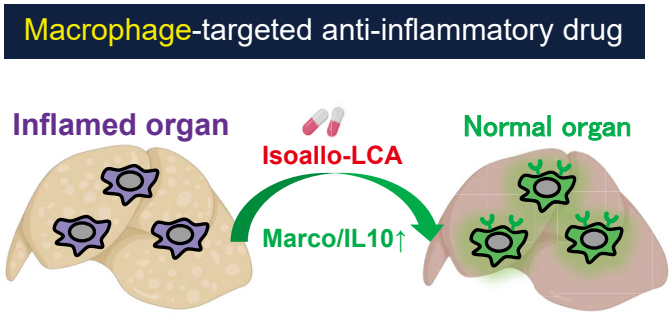

Fig. 2 Conceptual diagram of macrophage-targeted drug design using Isoallo-lithocholic acid (Isoallo-LCA)

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