論 文 要 旨

Glycoprotein Nonmetastatic Melanoma B(Gpnmb)-Positive Macrophages Contribute to the Balance between Fibrosis and Fibrolysis during the Repair of Acute Liver Injury in Mice

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Glycoprotein nonmetastatic melanoma B (Gpnmb), a transmembrane glycoprotein that is expressed in macrophages, negatively regulates inflammation. We have reported that Gpnmb is strongly expressed in the livers of rats fed a choline-deficient, L-amino aciddefined (CDAA) diet. However, the role of macrophage-expressed Gpnmb in liver injury is still unknown. This study aimed to clarify the characteristics of infiltrating macrophages that express Gpnmb, and the involvement of Gpnmb in the repair process in response to liver injury. C57BL/6J, DBA/2J[DBA] and DBA/2J-Gpnmb+ [DBA-g+] mice were treated with a single intraperitoneal injection of carbon tetrachloride (CCl4) at a dose of 1.0 mL/kg body weight. Mice were sacrificed at predetermined time points, followed by measurement of serum alanine aminotransferase (ALT) levels and histological examination. Expression of Gpnmb, pro-/anti-inflammatory cytokines, and profibrotic/antifibrotic factors were examined by quantitative RT-PCR and/or Western blotting. Immunohistochemistry, fluorescent immunostaining and flow cytometry were used to determine the expression of Gpnmb, CD68, CD11b and α-SMA, phagocytic activity, and the presence of apoptotic bodies. We used quantitative RT-PCR and ELISA to examine TGF-β and MMP-13 expression and the concentrations and supernatants of isolated infiltrating hepatic macrophages transfected with siGpnmb. In C57BL/6J mice, serum ALT levels increased at two days after CCl4 injection and decreased at four days. Gpnmb expression in the liver was stimulated four days after CCl4 injection. Histological examination and flow cytometry showed that Gpnmb-positive cells were almost positive for CD68-positive macrophages, contained engulfed apoptotic bodies and exhibited enhanced phagocytic activity. Isolated infiltrating hepatic macrophages transfected with siGpnmb showed high MMP-13 secretion. There was no significant difference in the magnitude of CCl4-induced liver injury between DBA-g+ and DBA mice. However, hepatic MMP-13 expression, as well as α-SMA expression and collagen production, increased significantly in DBA-g+ compared with DBA mice. Gpnmb-positive macrophages infiltrate the liver during the recovery phase of CCl4–induced acute liver injury and contribute to the balance between fibrosis and fibrolysis in the repair process following acute liver injury.