Deficiency of periostin impairs liver regeneration in mice after partial hepatectomy

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Abstract

Periostin (Postn) is a crucial extracellular remodeling factor that has been implicated in the pathogenesis of hepatic inflammation, fibrosis, non-alcoholic fatty liver disease and liver cancer. However, the role of Postn in liver regeneration remains unclear. Here, we demonstrate that *Postn* mRNA and protein levels are significantly upregulated in the mice after 2/3 partial hepatectomy (PHx). Compared with wild-type mice, *Postn*-deficient mice exhibit lower liver/body weight ratio and less Ki67-positive cells at days 2, 8 and 14 after PHx. Macrophage infiltration and the levels of *TNF-α*, *IL-6* and *HGF* in the livers of *Postn*-deficient mice are significantly decreased compared with wild-type mice one day after PHx. In addition, overexpression of Postn leads to higher liver/body weight ratio and more Ki67-positive cells in the livers of mice and promotes hepatocyte proliferation in vitro. Moreover, liver sinusoidal endothelial cells, biliary epithelial cells and hepatocytes can express Postn after PHx, and Postn deficiency impairs angiogenesis during liver regeneration. Our findings indicate that Postn deficiency impairs liver regeneration in mice after PHx and Postn might be a novel promoter for liver regeneration.

Introduction

The liver is a unique organ with remarkable regenerative potential, which allows restoration of liver mass after surgical resection, toxic exposure or viral injury [1–3]. Liver regeneration is a well-orchestrated and highly regulated process that is mediated by various cytokines, growth factors, hormones, reactive oxygen species and other stimuli. These stimuli induce the coordinated activation and proliferation of hepatocytes. Subsequently, the lost parenchymal liver mass recovers after several cycles of hepatocyte division. In addition to hepatocytes, other cells in the liver, such as liver sinusoidal endothelial cells (LSECs) and Kupffer cells, are also involved in liver regeneration [1–3]. Liver regeneration has significant clinical applications and deficient liver regeneration increases mortality risk. However, there is no therapeutic strategy established to accelerate liver regeneration. Therefore, a further understanding of the mechanisms of liver regeneration would provide a promising clinical benefit for accelerating liver regeneration.

Periostin (Postn) is a 90-kDa secreted matricellular protein that contributes to various diseases, such as skin inflammation, airway inflammation, atherosclerosis, tumorigenesis and metastasis [4–6]. Accumulating evidence indicates that Postn is a critical factor in the development of hepatic inflammation, fibrosis, non-alcoholic fatty liver disease (NAFLD), non-

alcoholic steatohepatitis (NASH) and liver cancer [7–12]. Postn levels are high in *ob*/*ob* mice, *db*/*db* mice and high-fat-diet-fed mice, as well as in NAFLD patients [7,11]. Our previous data demonstrated that Postn expression is significantly elevated in mice and patients with acute or chronic liver fibrosis and Postn deficiency ameliorates liver inflammation and fibrosis [9]. We further found that Postn is highly upregulated in methionine-choline-deficient (MCD) diet-induced NASH mice. Deficiency of Postn abrogates the development of MCD diet-induced NASH in mice [10]. The level of POSTN is also high in patients with liver tumors [12]. However, it is still unclear whether Postn contributes to liver regeneration.

Partial hepatectomy (PHx) in rodents is a well-known model for studying liver regeneration. In this model, two-thirds of the liver is removed without damage to the remaining lobes, which can enlarge to compensate for the mass of the removed portion of the liver [13,14]. In this report, we evaluated the level of Postn in the mice after PHx and further determined the role of Postn in liver regeneration after PHx using *Postn*-deficient mice. Our results showed that Postn is significantly upregulated in the livers of mice after PHx and Postn deficiency impairs liver regeneration in mice after PHx.

Results

Postn expression is elevated in the livers of mice after PHx

To determine whether Postn is involved in liver regeneration, we performed PHx on male C57BL/6 mice to induce liver regeneration. As determined by qRT-PCR, the expression of *Postn* in whole-liver lysates was increased after PHx. *Postn* mRNA levels were significantly elevated from day 3 to day 14 and peaked at day 6 in the livers of mice after PHx (Fig. 1A). Additionally, we found that Postn protein levels were upregulated in the livers of mice after PHx by western blotting analysis (Fig. 1B). Compared with the sham-operated control group (day 0), Postn staining became stronger in the livers of mice after PHx, even at 8 days and 14 days after PHx when the liver recovered its normal mass (Fig. 1C). These results suggest that *Postn* expression is upregulated at both the mRNA and protein levels in the livers of mice after PHx.

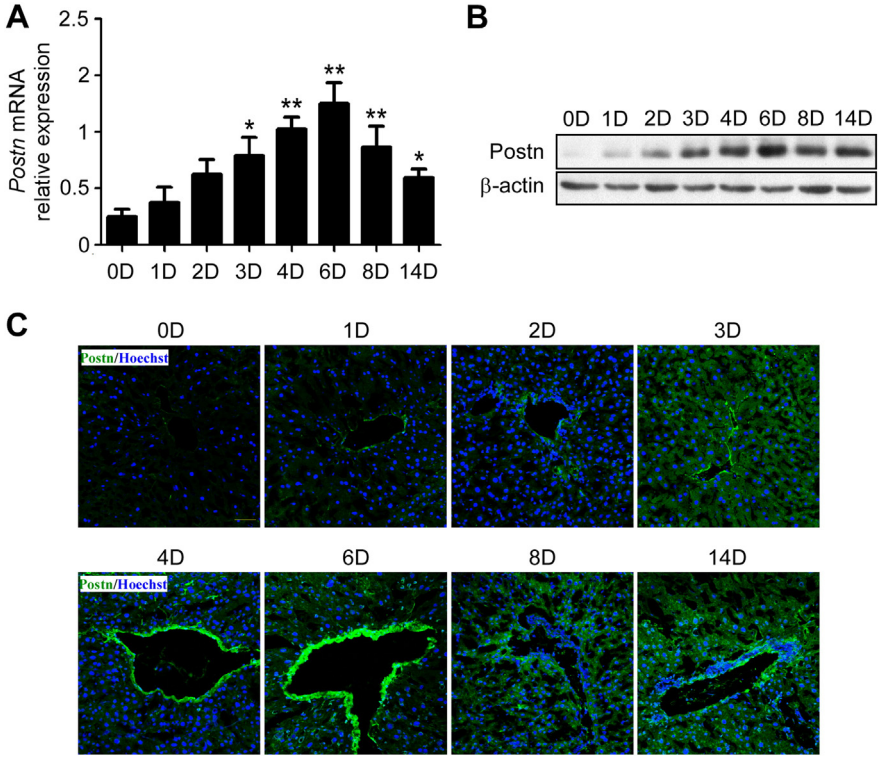

Fig. 1. *Postn* expression is increased in the livers of mice after PHx. The mRNA and protein levels of *Postn* in the livers of sham-operated (0D) mice and hepatectomized mice after PHx at different time points (1D–14D) were determined by qRT-PCR (A), western blotting (B) or immunofluorescent staining (C) analyses (n = 3–5 mice in each group). *$P < 0.05$, and **$P < 0.01$. Scale bar, 50 μm. The results are shown as the mean ± SEM.