Role of Leptin in Pathogenesis of NASH

KENICHI IKEJIMA, TIE LANG, SHUNHEI YAMASHINA, NOBUYUKI ENOMOTO, YOSHIYUKI TAKEI, and NOBUHIRO SATO

Summary. Increasing lines of evidence indicate that obesity is an important risk factor for the exacerbation of alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH). Leptin, an obese gene product, is a cytokine-type hormone mainly produced from adipose tissue. Recently, it has been demonstrated that serum leptin levels are increased in patients with alcoholic cirrhosis. In this study, therefore, we investigated the role of leptin in hepatic fibrogenesis. Activated hepatic stellate cells (HSCs) produced leptin during hepatic fibrogenesis. Xenobiotic-induced hepatic fibrogenesis was almost completely abolished in ob/ob mice and Zucker (fa/fa) rats, which are inborn leptin- and leptin receptor (Ob-R)-deficient animals, respectively. Further, leptin increased transforming growth factor (TGF)-β mRNA in isolated sinusoidal endothelial cells and Kupffer cells. Moreover, leptin augmented platelet-derived growth factor (PDGF)-dependent proliferation of HSCs. Taken together, these findings lead to the postulation that leptin acts as a profibrogenic cytokine in the sinusoidal microenvironment. In conclusion, leptin most likely plays a pivotal role in the progression of hepatic fibrosis in a variety of chronic liver diseases, including NASH.

Key words. NASH, Hepatic fibrogenesis, Leptin, Sinusoidal cells, TGF-β

Introduction

Accumulating lines of evidence suggest that alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH) share a common pathophysiological basis, in terms of inflammation and fibrogenesis. Because NASH is often associated with metabolic syndrome, comprising obesity, type-2 diabetes, and hypertension, it is hypothesized that adipocytokines, insulin resistance, and autonomic nervous regulation play causative roles in the disease progression of NASH. Leptin, an obese gene product mainly produced from adipocytes, is a cytokine-type hormone that regulates food intake and fat metabolism through actions on the central nervous system [1]. Recently, McCullough et al. [2] reported that serum leptin levels were increased in patients with alcoholic cirrhosis. Further, hepatic stellate cells (HSCs) have been shown to produce leptin when they become activated [3]. Moreover, the coadministration of recombinant
leptin augments the inflammation and fibrogenesis in the liver caused by hepatotoxic xenobiotics [4]. These findings lead to the hypothesis that leptin plays a pivotal role in profibrogenic responses in the liver.

Leptin receptors (Ob-R) were originally shown in hypothalamic neurons, through which leptin regulates food intake and body weight [5]. In fact, homozygous mutations of the leptin receptor gene have been identified in rodents (i.e., db/db mice and Zucker rats), which are also associated with obesity [6, 7]. There are several isoforms of Ob-R, which are splice variants with the same extracellular domain. The most ubiquitous form of Ob-R is a short-form receptor (Ob-Ra); however, the function of this receptor isoform remains unclear. In contrast, a long-form leptin receptor (Ob-Rb), which contains a longer intracellular domain, is known to activate the Janus kinase (JAK)-STAT-3 pathway, leading to the transcriptional regulation of target genes (Fig. 1). In the present study, we investigated the expression and functions of Ob-R in hepatic sinusoidal cells in order to elucidate the mechanisms underlying the profibrogenic action of leptin in the liver.

**Poor Hepatic Fibrogenesis in Leptin- and Ob-R-Deficient Animals**

In a previous study, we [4], demonstrated that administration of recombinant leptin augmented profibrogenic responses in the liver caused by xenobiotics (i.e., carbon tetrachloride and thioacetamide [TAA]) in mice. These observations led us to investigate whether endogenous leptin promoted hepatic fibrogenesis. To answer this question, we utilized ob/ob mice, which lack leptin due to naturally occurring disruption of the leptin gene. Interestingly, ob/ob mice demonstrate extremely poor profibrogenic responses to xenobiotic treatment [8], suggesting that leptin is one of the key regulators of hepatic fibrogenesis.