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Leptin in the Liver: A Toxic or Beneficial Mix?

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Abstract

Although obesity is associated with non-alcoholic fatty liver disease (NAFLD), the causal mechanisms are unclear. In this issue, Imajo et al. (2012) show that in mice leptin enhances the effects of bacterial endotoxin, promoting the development of NAFLD.

Nonalcoholic fatty liver disease (NAFLD) encompasses a range of liver disorders having increased intracytoplasmic triglyceride in hepatocytes (hepatic steatosis). As the term NAFLD implies, there is no identified cause of the hepatic steatosis, such as ethanol consumption or use of a steatotic medication. NAFLD without hepatocellular injury is termed nonalcoholic fatty liver (NAFL), while NAFLD with inflammation and hepatocyte injury is denoted nonalcoholic steatohepatitis (NASH) (Chalasani et al., 2012). In adults, the estimated prevalence of NAFLD worldwide is 20% and that of NASH is 4% (Vernon et al., 2011). It is not known what distinguishes those individuals with NAFL who will progress to NASH from those who are protected from progression. Similarly, it is unknown why some NASH patients progress to cirrhosis while most do not. Imajo et al. (2012) now identify a mechanism that promotes NASH in mice. They show that in a mouse model of steatosis, high leptin levels increase the levels of CD14, an innate immune receptor that recognizes bacterial lipopolysaccharide. High CD14 levels, in turn, promote inflammation, leading to NASH.

Given that obesity is the largest risk factor for increased liver triglyceride content, an increase in NAFL prevalence is expected from the current epidemic in obesity. Other risk factors for NASH include insulin resistance, increased low density lipoprotein cholesterol, and metabolic syndrome. However, the causal mechanisms explaining the relationship between NAFLD and these risk factors are not clear at this time (Cohen et al., 2011). This is in part due to the lack of clearly predictive animal models (Hebbard et al., 2011). From first principles, the steatosis could be due to increased fatty acids supplied by dietary intake, adipose tissue release, or *de novo* hepatic synthesis. Hepatic steatosis could also be due to reduced removal of triglyceride via fatty acid oxidation and/or export as very low density lipoprotein particles. The inflammatory component is similarly likely to be multifactorial, with causes both linked to steatosis and independent of it.

Imajo et al. (2012) studied a mouse model in which the steatosis is induced with a high fat diet (HFD) and the inflammatory state with bacterial lipopolysaccharide (LPS). They demonstrate that the HFD, in addition to increasing liver triglyceride, also increases CD14-

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positive Kupffer cell content. CD14 participates in innate immunity, acting as a receptor for and thus sensitizing cells to bacterial lipopolysaccharide (LPS). The HFD mice were treated with the highest dose of LPS that, in chow-fed controls, did not increase markers of liver injury. This same LPS dose did increase liver triglyceride content, pro-inflammatory cytokine expression, inflammatory cell infiltration, and fibrosis when given to the HFD mice. Furthermore, Imajo et al also show that the adipose-derived 'adipokine' hormone leptin increases Kupffer cell CD14 expression, whereas deficiency of leptin or leptin signaling protects against increased CD14 expression, liver inflammation and fibrosis. Taken together, the data support the paradigm that a HFD induces obesity and increases leptin levels, thereby increasing Kupffer cell CD14 levels and increasing sensitivity to LPS-mediated hepatic inflammation and injury.

Although leptin deficiency has a greater effect on metabolic parameters than does leptin excess, leptin's effects on immune responses and inflammation may not follow the same pattern. For example, the modest immune deficits of leptin-deficient patients do not cause a clinically significant immune deficiency phenotype (Farooqi et al., 2002). In contrast, Imajo et al. make a strong case for a permissive - even causal - contribution of leptin in their mouse NAFLD model. How general is this result--does it apply to human NAFLD? Consistent with their mouse observations, Imajo et al. present human data showing a correlation between hepatic CD14 mRNA levels and serum leptin levels. In a BMI-matched comparison, eight NASH patients had higher hepatic CD14 mRNA and serum leptin levels than did six non-NAFLD controls. However, at least seven papers have previously examined the correlation between circulating leptin levels and various measures of NAFLD in humans, and once the correlation between leptin and obesity is accounted for, there is no consistent link between leptin and NAFLD. Thus it remains unclear, from these observational studies, whether an increase in leptin levels actively promotes NASH.

Possibly the most direct test of leptin's role is the treatment of leptin-deficient NAFLD patients who suffer from lipodystrophy (Javor et al., 2005). Lipodystrophy patients have a genetically-, inflammatory-, or autoimmune-mediated deficiency of adipose tissue and thus low leptin levels. The paucity of adipose tissue also leads to ectopic triglyceride deposition, including hepatic steatosis. When leptin was administered to lipodystrophy patients with NASH, the liver disease improved dramatically, with six of eight patients no longer meeting the NASH diagnostic criteria, suggesting that in these cases leptin reversed the NASH. There are a number of possible explanations for the apparently opposite effects of leptin reported by Imajo et al. and by Javor et al. For example, the mouse LPS model of NASH may be a special case, mouse NASH may be fundamentally a poor model of human NASH, or the NASH in lipodystrophy may be unrepresentative of 'typical' NASH due to inadequate adipose tissue storage capacity. To determine which (if any) of these explanations is correct, will require a deeper understanding of NASH.

A starting point might be detailed phenotyping and classification of NAFLD using criteria in addition to medical history and histology. Comparison with cancer is illustrative—by exquisitely genotyping and phenotyping cancers, treatments can now be tailored, thus yielding a higher probability of treatment success and less toxicity. A similar analysis of NAFLD may identify sub-classes of the disease with unique immune, inflammatory and metabolic characteristics, and may reveal whether leptin plays the same or different roles in each type. Genetic screens have now identified six loci that contribute to variance in NAFLD traits (eg, Romeo et al., 2008; Speliotes et al., 2011), with one increasing hepatic triglyceride production (Kumari et al., 2012), suggesting that further phenotyping efforts will be fruitful. It seems likely that integrating phenotypic and genetic information with mechanistic studies will help unravel the conundrum that is NASH. In summary, Imajo et al. make a strong case that leptin contributes to NASH in a mouse endotoxin model of NASH.

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This interesting result will spur examination of the generality of the contribution of leptin in other NASH models and drive more detailed mechanistic studies of NAFLD.

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