

Editorial

Understanding the Pathogenesis of Insulin Resistance in Non-Alcoholic and Alcoholic Liver Diseases

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Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) cause significant morbidity and mortality in affected patients and are common causes of liver failure worldwide [1]. NAFLD and ALD are histologically indistinguishable by conventional methods but their disease courses are quite divergent. In particular, ALD patients with steatohepatitis have a more rapid progression to advanced liver disease than NAFLD patients with steatohepatitis [2].

Our research program is focused on understanding both the similarities and differences between the biology of NAFLD and ALD using experimental models. Specifically, we employ both genetic mouse models and cellular models to investigate how lipids and their associated proteins cause insulin resistance, a known predictor of disease progression in both NAFLD and ALD.

We have thus far demonstrated a key role of lipid droplet proteins in the pathogenesis of insulin resistance in both NAFLD and ALD experimental models. Lipid droplet proteins are proteins associated with the phospholipid monolayer of lipid droplets [3]. In the liver, the Perilipin family of lipid droplet proteins predominates [4]. We have demonstrated that these lipid droplet proteins have important functions in energy homeostasis including in reducing glucose and insulin sensitivity [5,6]. Perilipin 2 (Plin2) is the predominant hepatic Perilipin protein, and Perilipin 1 (Plin1) is *de novo* expressed in human NAFLD [4]. In a small pilot study examining liver sections from adults and children with hepatic steatosis, we observed an increase in Plin1 and Plin2 immunostaining in patients with non-alcoholic steatohepatitis (NASH) compared with NAFLD simple steatosis and non-steatotic control sections. Moreover, Plin1 expression correlated with NASH but not Hepatitis C, a common steatohepatic disease [7]. In our experimental ALD model, we observed an upregulation of Plin2 in whole liver lysates of ethanol-fed mice. Upregulation of Plin2 coincides with the onset of hepatic steatosis, glucose intolerance and insulin resistance [8]. Plin2 is also a reliable lipid droplet marker in alcohol fed rats [9], in mice fed a high fat, ethanol diet [10], and in WIF-B cells treated with oleate and ethanol [11]. Our ongoing research aims to understand the mechanisms by which lipids and lipid droplet proteins promote insulin resistance in NAFLD and ALD.

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One mechanism by which lipids may promote insulin resistance in NAFLD and ALD is through the action of so-called "toxic" lipid metabolites. In NAFLD, the lipid metabolites diacylglycerol, ceramides, lysophosphatidic acid and fatty acyl CoA have been associated with impaired insulin signaling independent of triglyceride accumulation [12-17]; while in ALD, ceramides are suspected [18,19]. Indeed, our research shows an increase in diacylglycerol and ceramides in experimental NAFLD and ALD, respectively [5,8]. Diacylglycerol impairs insulin signaling through activation of PKC- ϵ activation and reduced IRS-2 tyrosine phosphorylation [20]; while ceramides, through their activation of protein phosphatase 2A, inhibit the phosphorylation of Akt, a key downstream event in insulin signaling [21,22]. Our research program will further investigate the specific role of these lipid species in the pathogenesis of NAFLD and ALD.

Success of our research program will be measured by the identification of key mediators of insulin resistance in NAFLD and ALD which can ultimately be used as both diagnostic tools for the pathologic distinction of NAFLD and ALD and as therapeutic targets for the amelioration of disease in NAFLD and ALD patients.

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