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Hepatic insulin resistance ties cholesterol gallstone formation and the metabolic syndrome

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Abstract

Biddinger SB, Haas JT, Yu BB, Bezy O, Jing E, Zhang W, Unterman TG, Carey MC, Kahn CR. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nature Medicine 2008; 14: 778–782.

Despite the well-documented association between gallstones and the metabolic syndrome,[1,2] the mechanistic links between these two disorders remain unknown. Here we show that mice solely with hepatic insulin resistance, created by liver-specific disruption of the insulin receptor (LIRKO mice)[3] are markedly predisposed toward cholesterol gallstone formation due to at least two distinct mechanisms. Disinhibition of the forkhead transcription factor FoxO1, increases expression of the biliary cholesterol transporters Abcg5 and Abcg8, resulting in an increase in biliary cholesterol secretion. Hepatic insulin resistance also decreases expression of the bile acid synthetic enzymes, particularly Cyp7b1, and produces partial resistance to the farnesoid X receptor, leading to a lithogenic bile salt profile. As a result, after twelve weeks on a lithogenic diet, all of the LIRKO mice develop gallstones. Thus, hepatic insulin resistance provides a crucial link between the metabolic syndrome and increased cholesterol gallstone susceptibility.

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Comment

Gallstone formation is a complex disorder that results from interactions between a genetic susceptibility and environmental factors such as type of diet, number of pregnancies, rapid weight loss and certain medications.[1] In addition, studies in different human populations confirmed an association of serum insulin levels and insulin-resistance with the risk of gallbladder disease.[2-5] Insulin resistance is believed to play a central role for the development of the so-called metabolic syndrome. However, the molecular links between insulin resistance and gallstone formation remained elusive.

Insulin resistance is present when the biological effects of insulin are less than expected, particularly in skeletal muscle, liver and adipose tissue. To further dissect the association of gallstone formation and insulin resistance, Biddinger *et al.* employed a mouse model with a deficiency of the hepatic insulin receptor only.[6] This mouse model displayed a number of features of the metabolic syndrome including hyperinsulinemia, hyperglycemia, increased hepatic gluconeogenesis and dyslipidemia.[7,8] When fed a lithogenic diet that contains high amounts of cholesterol and cholic acid and promotes cholesterol gallstone formation in susceptible inbred mouse strains, mice with a disrupted hepatic insulin receptor displayed higher cholesterol gallstone prevalence rates and developed cholesterol gallstones more rapidly than control mice. To identify the molecular mechanisms that predispose to gallstone formation, the authors further characterized the mice with a disrupted hepatic insulin receptor after the consumption of chow. They found decreased bile acid synthesis rates and a more hydrophobic bile salt pool in mice with hepatic insulin resistance.

The authors attributed this finding to decreased expression of the *Cyp7b1* gene after activation of the bile salt receptor FXR. *Cyp7b1* encodes the oxysterol-7α-hydroxylase that controls the acidic pathway of bile salt synthesis that in mice leads to the production of the hydrophilic bile salt muricholate. Increased hydrophobicity of the bile salt pool is known to promote gallstone formation and this appears to be the first mechanism of gallstone susceptibility in mice that are deficient of the hepatic insulin receptor. Interestingly, we recently found that polymorphisms of *NR1H4*, the gene encoding FXR, are associated with gallstone prevalence in selected human populations, suggesting that variation of FXR may predispose to gallstone formation by altering bile salt synthesis.[9]

In addition to the more hydrophobic bile salt pool, the authors found the gallbladder bile of hepatic insulin receptor-deficient mice to be slightly supersaturated with cholesterol after the consumption of chow. This finding was explained by higher biliary cholesterol secretion rates of cholesterol in knockout compared to control mice that resulted from increased expression levels of the heterodimeric cholesterol transporter ABCG5/ABCG8. As one molecular link between hepatic insulin resistance, increased ABCG5/ABCG8 expression and higher biliary cholesterol secretion rates, the authors identified FoxO1. The transcription factor FoxO1 is inhibited by insulin through phosphorylation and this, in turn, leads to decreased expression levels of key enzymes in gluconeogenesis and reduced hepatic glucose production.[10] The authors showed *in vitro* that FoxO1 increases expression of ABCG5/ABCG8 and confirmed these findings *in vivo* employing a *FOXO1* transgenic mouse model. In addition, the authors identified a putative FoxO1 binding site in the genomic segment that separates the transcription start sites of *Abcg5* and *Abcg8,* which are located side-by-side in a head-to-head configuration on mouse chromosome 17 and human chromosome 2, respectively. These findings suggest that hepatic insulin resistance leads to impaired phosphorylation and inactivation of FoxO1, which in turn increased expression levels of ABCG5/ABCG8 and promotes biliary cholesterol secretion and predisposes to gallstone formation. Increased hepatic expression levels of *ABCG5/ABCG8* were previously found to be associated with susceptibility to cholesterol gallstone formation in the inbred mouse model of cholelithiasis[11,12] and in humans with gallstones.[13] Furthermore, a polymorphism of *ABCG8* was confirmed to be associated with gallstone formation in human populations[14,15] underscoring a key role of the ABCG5/ABCG8 heterodimer in the pathophysiology and genetic susceptibility to gallstone formation. It is also noteworthy that recent studies reported associations of *FOXO1* genetic variants with type 2 diabetes and related traits in distinct Caucasian populations.[16,17]

In summary, Biddinger *et al.* provide the first molecular insight into the connection between insulin resistance and cholesterol gallstone formation. The findings suggest that FoxO1 is a promising target for cholesterol gallstone prevention and should prompt genetic studies in humans to dissect the genetic connections between insulin resistance and gallstone susceptibility.

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