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Regulation of Retinol-Binding Protein 4 and Retinol Metabolism in Fatty Liver Disease

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Vitamin A refers to a spectrum of retinoid compounds (retinol, retinoic acid, and retinaldehyde) with important functions in different tissues, including the retina and skin. Retinoids regulate metabolic pathways through binding to two nuclear hormone receptors: retinoic acid receptor and retinoid X receptor.[1] In humans, approximately 80% of the body reservoir of vitamin A is stored in the liver as retinyl ester in hepatic stellate cells (HSCs). Upon physiological cues, retinoids are released in a controlled fashion and bind to retinol-binding protein 4 (RBP4) in the circulation. Retinoids are also released by activated HSCs during liver damage; activation of these cells plays a key role in progression of liver damage and fibrogenesis,[2] but the consequence of the retinoid release under these circumstances is poorly understood.

Changes in RBP4 levels seem to play a role in nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome (MetS) and, now, the leading cause of liver damage.[3] Indeed, epidemiological studies have shown that higher RBP4 levels are associated with MetS and NAFLD.[4] Moreover, changes in RBP4 levels may contribute to insulin resistance (IR)[5] and liver steatosis (LS) by influencing hepatic *de novo* lipogenesis.[6] However, the mechanisms linking increased RBP4 with NAFLD are unknown.

In this issue, Lee et al. describe a new transgenic mouse model overexpressing human RBP4 specifically in the adipose tissue (adi-hRBP4 mice).[7] The highlight of this study is to test *in vivo* the hypothesis that ectopic human RBP4 overexpression in the adipose tissue can influence hepatic steatosis (HS). When fed a high-fat diet, adi-hRBP4 mice showed higher susceptibility to HS as a result of adipose tissue inflammation, IR, and increased free fatty acid (FFA) flux to the liver. These mice also had reduced glucose tolerance and thus exhibited the features of MetS associated with NAFLD. This phenotype did not appear to be dependent on overt alterations of retinoid metabolism. The importance of this work resides in showing how intracellular overexpression of RBP4 in adipose tissue results in a redistribution of fat from the adipose to the liver by activating lipases and promoting inflammation. The investigators propose that liver disease starts when RBP4 levels increase in the adipose tissue and that increased circulating RBP4 levels are a consequence, and not a cause, of disease. This model would be consistent with the fact that a specific RBP4-dependent intracellular signaling pathway mediating the effects of circulating RBP4 has not been identified.

However, a limitation of this work is that body weight was higher in the adi-hRBP4, compared to the

Abbreviations: FFA, free fatty acid; HS, hepatic steatosis; HSCs, hepatic stellate cells; IR, insulin resistance; LS, liver steatosis; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; PNPLA3, patatin-like phospholipase domain-containing 3; RBP4, retinol-binding protein 4.

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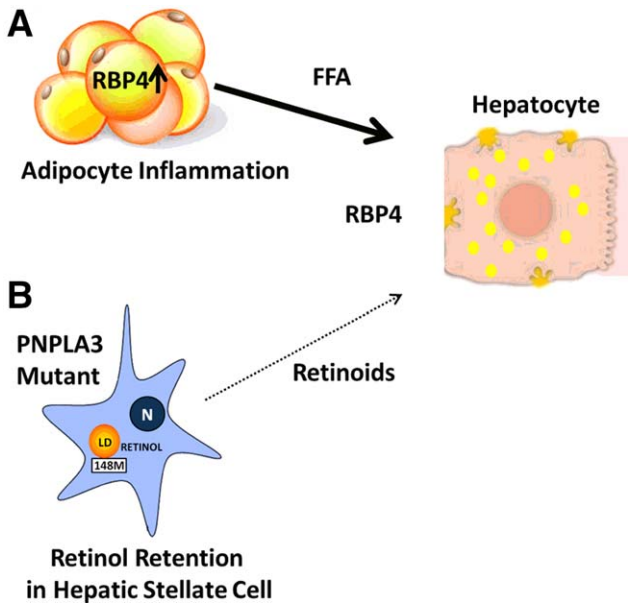

FIG. 1. Disease model for intracellular hepatocyte lipid accumulation. (A) Overexpression of RBP4 determines adipocyte inflammation and redistribution of lipids through an excess of flux of FFAs from the adipocyte to the hepatocyte. (B) Carriers of the PNPLA3 148M mutation have intracellular retention of retinoids in HSCs, causing the increase in hepatocyte intracellular lipid content. In both models, circulating RBP4 levels represent a biomarker of disease. Abbreviations: LD, lipid droplets; N, nucleus.

wild-type, mice, which could contribute to ectopic liver fat accumulation.

How do these data fit in the present understanding of the role of retinol metabolism in the progression from NAFLD to advanced liver disease? Human and molecular genetics may provide some clues. Indeed, a body of evidence indicates that the I48M variant of patatin-like phospholipase domain-containing 3 (PNPLA3) is the major human genetic determinant of LS and subsequent disease progression to cirrhosis and hepatocellular carcinoma.[8] We have shown that PNPLA3 is responsible for the release of retinol from HSCs and that the PNPLA3 mutation induces retinoid intracellular retention.[9,10] Carriers of the PNPLA3 mutation have more-severe liver damage, retinoid retention in the liver, and lower levels of circulating retinol and RBP4.[9,10]

We therefore speculate that there are at least two disease models for NAFLD susceptibility: (1) one where intracellular increase of RBP4 in the adipose tissue causes inflammation and redistribution of fat to the liver through an increased fatty acid influx and (2) one genetically driven where the PNPLA3 mutation causes intracellular retinol retention in HSCs and therefore lower levels of RBP4 in the circulation (see Fig. 1). In the first model, retinol would not influence liver disease whereas in the second the disease would be driven by actual retinol availability. In both cases, circulating RBP4 would represent only a biomarker of disease and not a causal factor.

In conclusion, this study shows that increased intracellular RBP4 availability determines ectopic fat excess in the liver by increased FFA influx to this organ from the adipose tissue. The RBP4-retinol metabolism is complex, and more studies are needed to understand the intricate relationship between RBP4 and retinol in causing liver disease.

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