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EDITORIAL

Bile Acids: The Hidden Gateway Behind Autophagy Modulation in the Liver

In 2016 the Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for his discoveries of mechanisms for autophagy. This has been the highest accolade to this field, which started developing 50 years ago when De Duve coined the termed *autophagy*.[1] Since the early birth of this field, autophagy has been linked intimately to liver metabolism. Autophagy is an essential recycling mechanism that ensures an equilibrium between synthesis and degradation of intracellular components. During the 50 years since its first description, autophagy has been shown to be involved in a multitude of cellular processes and degrade very diverse cellular components ranging from organelles, proteins, or glycogen to lipids.[1] Recently, there has been increasing interest in the field of metabolism to understand the role of autophagy in the catabolism of lipid, an essential process for the maintenance of cellular and organismal energetics.

Nutrient availability controls autophagic rates through diverse, but complementary, signaling pathways. The mechanistic target of rapamycin (mTOR) is one of the best known regulators of autophagy. mTOR inhibition, resulting from a shortage of nutrients, leads to activation of macroautophagy, one of the best-characterized types of autophagy.[2] The effectors of this complex system are the autophagy-related proteins (ATGs), which are involved in every step of this recycling system. To control and respond adequately to environmental challenges there are various signaling pathways involved in ATG regulation. One of the master regulators of this signaling is the transcription factor EB, which monitors autophagy through transcriptional regulation of ATGs and vesicular trafficking proteins, but it also monitors lysosomal biogenesis.[3,4] In the fed state the sensing nuclear receptor farnesoid X receptor controls the basal recycling of proteins, whereas in the absence of nutrients the cyclic adenosine monophosphate response element-binding protein and peroxisome proliferator-activated receptor-α[5,6] take control to switch the preferred cargo from proteins to the degradation of lipids by autophagy or lipophagy.[7]

The liver is the main site for cholesterol biosynthesis and therefore adequate cholesterol regulation is critical to avoid metabolic dysfunctions that result in pathologies such as fatty liver, diabetes, or atherosclerosis. A critical step in cholesterol homeostasis is the regulation of bile acid synthesis. Because bile acids are derived from cholesterol, an increase in bile acid synthesis results in a decrease in the intracellular pool of cholesterol. The master regulator in cholesterol content is the endoplasmic reticulum–bound protein Sterol regulatory element-binding protein-2 (SREBP-2), which gets activated in response to diminished intracellular levels of sterols. SREBP-2 nuclear translocation results in an increased uptake (low-density lipoprotein [LDL] receptor) and biosynthesis (3-hydroxy-3-methylglutaryl–coenzyme A reductase) of cholesterol to replenish its intracellular levels. Hence, chemical or genetic approaches that activate bile acid synthesis are useful to mobilize not only the intracellular content of cholesterol, but also the circulating levels of LDLs. A critical step within this network is the endoplasmic reticulum resident enzyme cholesterol 7-alpha-monooxygenase (CYP7A1), which converts cholesterol into bile acids. Given the exponential increasing prevalence of metabolic diseases related to dyslipidemias, new therapeutic targets such as CYP7A1 are of extraordinary interest. To date, the drugs most commonly used for the treatment of dyslipidemias are the worldwide statins (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibition) and the bile acid sequestrants (increase excretion of bile acids that results in increased bile acid synthesis). The connection between the axis bile acids/cholesterol and liver autophagy until now had remained unexplored.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Wang et al[8] nicely show the different effects of free cholesterol (FC) and LDLs on autophagy activity. FC impairs autophagic flux to a greater extent than that of LDLs, which contain mainly cholesterol esters. This impairment is caused by a blockage in the vesicle fusion between the autophagosome and the lysosome. FC loading associates with the appearance of enlarge abnormal lysosomal structures, decreased lysosomal activity, and increased lysosome membrane permeabilization. In an effort to revert the inhibitory effect of FC loading in autophagy, Wang et al[8] chemically induced bile acid synthesis *in vivo* by feeding mice with the bile acid sequestrant cholestyramine (ChTM). The treatment with ChTM decreased FC and farnesoid X receptor target genes and increased the limiting enzyme CYP7A1 and bile acid intermediates. ChTM treatment markedly increased the liver content of the autophagy effector LC3-II, while decreasing levels of the autophagy substrate p62. These findings, along with the higher abundance of autophagosomes and reduced AKT/mTOR activity observed in the livers of ChTM-treated mice, are suggestive of a stimulatory effect of this intervention on autophagy. To decipher the molecular mechanisms behind this activation of autophagy, Wang et al[8] genetically modulated CYP7A1 in rat hepatocytes. The authors elegantly showed that genetic up-regulation of the limiting enzyme in bile acid synthesis results in SREBP-2 activation and autophagy flux up-regulation, associated with an inhibition of the mTOR signaling pathway. This inhibition comes only from the cell surface and is independent of amino acid signaling in the lysosomes. Finally, as a therapeutic proof of concept, they restore hepatic autophagy through increased bile acid synthesis in a mouse model of

diet-induced obesity. Only 3 weeks of ChTM feeding decreased body weight, hepatic triglycerides and cholesterol, and total plasma cholesterol levels in these mice. As anticipated, mice fed a Western diet but with ChTM showed increased levels of LC3-II and *in vivo* experiments using the Red Fluorescent Protein-Green fluorescent protein-LC3 (RFP-GFP-LC3) autophagy tandem reporter confirmed increased autophagy flux in these cells.

This work highlights important aspects previously undervalued in this field such as the higher inhibitory effect on autophagy of free cholesterol when compared with cholesterol esters and the value of the axis CYP7A1/AKT/mTOR as a potential candidate for inducing autophagy in the liver through bile acid synthesis modulation. Bile acid signaling usually has been underestimated as a possible therapeutic target for metabolic diseases, but this study clearly emphasizes its potential.

Therefore, this study opens new avenues for the therapeutics of liver and cholesterol-related diseases through manipulation of bile acid synthesis. It would be interesting to explore whether drugs that modulate bile acid signaling such as apical sodium dependent bile acid transporters also could be used to modulate autophagy in the liver. Because bile synthesis is performed only by hepatocytes, the modulation of bile acid signaling could be a promising approach for highly selective targeting of autophagy in the liver.

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