

## Endoplasmic Reticulum Stress Emerges as Novel Regulator for Bile Acid Synthesis



Bile acids are amphipathic molecules synthesized from cholesterol in the liver, and bile acid synthesis represents the most critical mechanism to remove cholesterol from the body. Bile acids are known to undergo enterohepatic circulation, and in the small intestines they facilitate the absorption of lipids and lipid-soluble vitamins. Bile acids have also emerged as important signaling molecules in regulating energy metabolism, lipid homeostasis, and inflammation via interaction with nuclear receptors (farnesoid X receptor [FXR], pregnane X receptor, and vitamin D receptor) and G-protein coupled membrane receptors (G-protein coupled bile acid receptor 1–TGR5 and sphingosine 1-phosphate receptor 2). Because bile acids can cause cellular damage in some circumstances, bile acid synthesis is precisely regulated by an orchestral interplay of various transcription factors and signaling molecules. Two pathways determine bile acid synthesis in the liver, the classic and the alternative pathway, mediated by the rate limiting enzymes cholesterol 7 $\alpha$  hydroxylase and cholesterol 27 $\alpha$  hydroxylase, which are encoded by *Cyp7a1/CYP7A1* and *Cyp27a1/CYP27A1*, respectively. Transcriptional regulation of *Cyp7a1/CYP7A1* gene expression is critical for maintaining bile acid homeostasis, and the nuclear receptor FXR, which is activated by bile acids, is the most important suppressor of bile acid synthesis under physiological conditions. Activated FXR suppresses bile acid synthesis via hepatic induction of the small heterodimer partner (SHP) and intestinal induction of fibroblast growth factor (FGF) 15 (human FGF19). *Cyp7a1/CYP7A1* gene expression is also subject to regulation by hepatic nuclear receptor 4 $\alpha$ , thyroid hormone receptor, glucocorticoid receptor, inflammatory cytokines, insulin receptor activation, microRNAs, FOXO1, and circadian rhythms, indicating a critical need for precise regulation of bile acid levels under both physiological and pathologic conditions.

The study by Henkel et al<sup>1</sup> shows that endoplasmic reticulum (ER) stress suppresses *Cyp7a1/CYP7A1* gene expression independent of its effects on FXR in the liver or gut, because ER stress in both mice and human hepatoma cell lines suppressed *Cyp7a1/CYP7A1* gene expression without altering the mRNA levels of SHP and/or FGF15. Furthermore, although inflammatory cytokines are known to suppress *Cyp7a1/CYP7A1* expression, this study shows instead that levels of cytokine expression in mice undergoing ER stress are decreased. In the setting of ER stress, the liver tries to maintain a bile acid–low status, as revealed by increased expression of the bile acid efflux transporters *Abcb11* and *Abcc3*, which pump bile salts out of the liver into the bile duct and blood, respectively, as well as by markedly reduced expression of *Slc10a1*, the major bile acid

uptake transporter responsible for transporting bile salts into the liver from the portal circulation. As a consequence, prolonged ER stress reduces the bile acid content in the liver.

Although it is possible that the suppression of *Cyp7a1/CYP7A1* gene expression is a direct effect of activation of the unfolded protein response, it is also possible that ER stress alters the post-translational modification of SHP or FGF15. This was not examined in this study. In addition, many of the other factors mentioned above that are critical in regulating *CYP7A1/Cyp7a1* gene expression may be altered at the mRNA or protein levels. The authors also speculate that IRE1 $\alpha$ -dependent mRNA decay is a mechanism responsible for the suppression of this critical gene involved in bile acid metabolism.

In summary, this study reports the significant finding that ER stress is a novel regulator of the classic bile acid synthetic pathway. This is important because impaired bile acid metabolism has been implicated in the pathogenesis of diabetes and obesity, both of which are associated with ER stress. In the future, efforts are needed to (1) determine the underlying molecular mechanisms by which ER stress suppresses bile acid synthesis and (2) provide experimental evidence that modulation of ER stress and bile acid homeostasis contribute to the pathogenesis of liver diseases.

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1. Henkel AS, LeCuyer B, Olivares S, et al. Endoplasmic reticulum stress regulates hepatic bile acid metabolism in mice. *Cell Mol Gastroenterol Hepatol* 2017;3:261–271.

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### Conflicts of interest

The author discloses no conflicts.

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