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EDITORIAL

Gender and Age Differences in the Hepatic Consequences of "Humanized" Bile Acid Compositions in Mice

Bile acids (BA) are increasingly being appreciated beyond their lipid solubilizing properties as complex signaling molecules that are intricately involved in the regulation of metabolic homeostasis. Accumulation of BAs is also known to be a driving force behind cholestatic liver injuries.[1,2] Although mouse models have long been used to study important aspects of BA metabolism, there are substantial differences between humans and mice in terms of BA pool composition and signaling potential, highlighting the difficulties in directly extrapolating mice findings to BA-related liver diseases in humans.[3] For example, compared with humans, rodents possess a significantly more hydrophilic BA pool because of the abundant presence of muricholic acids, a set of primary BAs hydroxylated at the 6-β position, making them much more water-soluble and less injurious. This, along with other species differences in BA composition, may explain why murine models of cholestasis fail to recapitulate the totality or severity of human diseases, and points to the urgent need to develop mouse models with "humanized" BA pool.

A recent landmark study published in the *Journal of Lipid Research* using *Cyp2c*-cluster null (*Cyp2c* null) mice followed by cellular recombinant analyses identified CYP2C70 as the enzyme necessary for the formation muricholic acids.[4] These *Cyp2c* null mice possessed a more human-like and hydrophobic BA profile. Two subsequent studies using CRISPR/Cas9-generated *Cyp2c70* knockout mice further confirmed the importance of this enzyme in the synthesis of 6-hydroxylated BAs and provided some surprising insights into how "a more humanized" BA composition impacts BA homeostasis and signaling. For example, increased levels of chenodeoxycholic acid observed in *Cyp2c70*-deficient mice as a result of blocking its conversion to muricholic acid did not lead to stronger farnesoid X receptor activation as expected because chenodeoxycholic acid is the most potent endogenous farnesoid X receptor activator[5]; instead, the cytokine and c-Jun N-terminal kinase signaling pathway was activated, potentially leading to the transaminitis and hepatic inflammation observed in these animals.[6,7]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, de Boer et al[8] further interrogated the pathophysiological consequences of global *Cyp2c70* deletion in mice from age- and gender-specific perspectives. Their comprehensive analyses showed that although male and female CYP2C70-deficient mice expectedly possessed more hydrophobic BA pools than their wild-type littermates, they displayed marked gender differences in the development of liver diseases. Although young *Cy2c70*$^{-/-}$ mice of both sexes exhibited several features of "neonatal cholestasis," as evidenced by elevated plasma BA levels, transaminitis, cholangiocyte proliferation, and increased hepatic expression of inflammatory markers, those abnormalities spontaneously improved in the males. Female mice, however, had persistent and progressively worsening hepatic dysfunctions with eventual progression of liver pathology to bridging fibrosis at advanced age. In addition to the hepatic aberrations, the authors also found impaired intestinal barrier function in female mice lacking CYP2C70 without any increase in endotoxin concentration in the portal plasma.

Given the complex interplay between the gut microbiome and BA signaling, the authors also examined the impact of CYP2C70 deficiency on bacterial colonization of the gut by 16S DNA sequencing. Specifically, they found in a cohort of male mice that the more hydrophobic BA composition is associated with distinct alterations in the cecal bacterial species that resemble those observed in patients with primary biliary cholangitis, including strong reduction in the genera of *Akkermansia*, which has been shown to promote intestinal barrier integrity.[9] It would also be interesting to characterize the microbial signature of the female *Cyp2c70*$^{-/-}$ mice in the future because primary biliary cholangitis predominately affects females.

To examine if the more hydrophobic BA profile in *Cyp2c70*$^{-/-}$ mice was responsible for the hepatic dysfunction and compromised intestinal barrier, the authors supplemented the mice chow to a cohort of female mice with ursodeoxycholic acid for 8 weeks. They found that the hydrophilic ursodeoxycholic acid normalized the aberrations, in part via amelioration of endoplasmic reticulum stress, suggesting that BA hydrophobicity indeed plays a contributory role in the development of liver diseases and further supporting the role of ursodeoxycholic acid as a chemical chaperone.[10]

Overall, this comprehensive and detailed study shows that the impact of *Cyp2c70* deficiency is significantly more pronounced in female mice compared with males, and the liver pathology progresses with age. It is also clear from this study, along with other recently published findings, that the effects of a more human-like BA profile on BA homeostasis and signaling in mice are complex and can be unexpected, especially in its effect on farnesoid X receptor signaling.[6–8] Although these mutant mice, in crossing breeding with other genetic mouse models, may serve as a valuable tool to study BA-related human liver diseases, such as neonatal cholestasis and primary biliary cholangitis, their role in modeling metabolic diseases remains to be seen given the baseline liver abnormalities. What also remains to be determined is the mechanism driving these

sex differences and if there is any gender difference in the intestinal microbiome that contributes to the phenotypical variations.

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