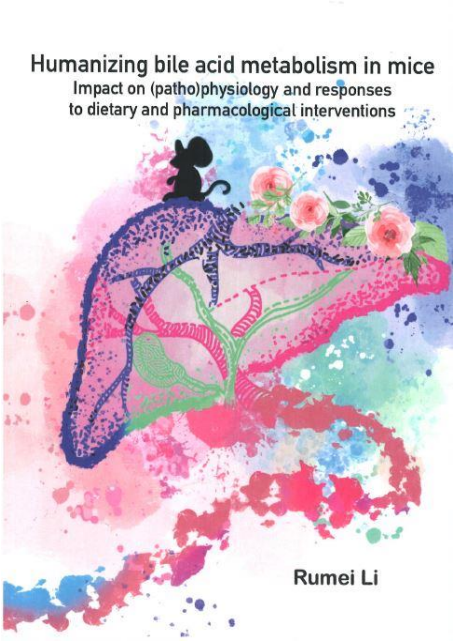

Samenvatting proefschrift
R. Li
'Humanizing bile acid metabolism in mice Impact on (patho)physiology and responses to dietary and pharma-cological interventions'

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Promotor:
Prof. F. Kuipers Dr. J. F. de Boer

Copromotor:
Dr. E.T.T.L. Tjwa

Bile acids (BAs) play important roles in lipid, glucose and energy homeostasis and BA signaling pathways may serve as therapeutic targets for human diseases, such as non-alcoholic fatty liver disease. However, translation of promising mechanistic pre-clinical data is hampered by marked species differences in BA metabolism. Rodent-specific muricholic acids (MCAs) exert entirely different actions on BA receptors compared to the BA species present in humans. To allow evaluation of the interconnections between BAs and human diseases, we aimed to gen-erate mice with a human-like BA composition by knocking out the *Cyp2c70* gene, which is responsible for MCA production in mice. Next, we characterized these mice with respect to BA metabolism and intestinal lipid absorption and delineated the (patho)physiological conse-quences of the hydrophobic BA composition in these mice, with a major focus on the liver. *Cyp2c70*-deficiency in mice did indeed prevent the production of MCAs. The hydrophobicity of the BA pool in *Cyp2c70*-deficiency mice was comparable to the human BA pool. *Cyp2c70*-deficient mice were protected from hepatic steatosis when fed a western type diet, which could be attributed to a reduction of intestinal fat absorption. Our data point to a crucial role of 12α-hydroxylated BAs in fat absorption.
The hydrophobic BA pool impacted the pathophysiology of the liver in *Cyp2c70*-deficient mice as cholangiopathic features were observed. Subsequently, the effects of selected pharmacolog-ical interventions that may hold potential for the treatment of cholangiopathies were explored in *Cyp2c70*-deficiency mice. Ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are the FDA-approved first- and second-line treatment options for patients with primary biliary cholangitis, while fisetin is a natural senolytic that has been shown beneficial effects in a mouse model with cholangiopathy. Our data showed that UDCA treatment could restore the chol-angiopathy, while OCA and fisetin treatment had limited effects on fibrosis in *Cyp2c70*-deficient mice. The human-like BA profile and the presence of cholangiopathy make *Cyp2c70*-deficienct mice a useful model to investigate potential therapeutic approaches for cholangiopa-thies.

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