5-Cholen-3\(\beta\),25-diol 3-sulfate decreases lipid accumulation in diet-induced nonalcoholic fatty liver disease mouse model

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Background & Aims: Sterol regulatory element binding protein-1c (SREBP-1c) increases lipogenesis at the transcriptional level and its expression is up-regulated by liver X receptor (LXR\(\alpha\)). The LXR\(\alpha\)/SREBP-1c signaling may play a crucial role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). We previously reported that a cholesterol metabolite, 5-cholen-3\(\beta\),25-diol 3-sulfate (25HC3S), inhibits the LXR\(\alpha\) signaling and reduces lipogenesis by decreasing SREBP-1c expression in primary hepatocytes. The present study aims to investigate the effects of 25HC3S on lipid homeostasis in diet-induced NAFLD mouse models.

Methods: NAFLD was induced by high fat diet (HFD) feeding in C57BL/6j mice. The effects of 25HC3S on the lipid homeostasis, inflammatory responses and insulin sensitivity were evaluated after acute treatments or long-term treatments.

Results: Acute treatments with 25HC3S decreased serum lipid levels, and long-term treatments decreased hepatic lipid accumulation in the NAFLD mice. Gene expression analysis showed that 25HC3S significantly suppressed the SREBP-1c signaling pathway which was associated with the suppression of the key enzymes involved in lipogenesis: fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC1) and glycerol-3-phosphate acyltransferase (GPAM). In addition, 25HC3S significantly reduced HFD-induced hepatic inflammation as evidenced by decreasing tumor necrosis factor (TNF\(\alpha\)) and Interleukin 1 (IL1\(\alpha/\beta\)) mRNA levels. Glucose tolerance test (GTT) and insulin tolerance test (ITT) showed that 25HC3S administration improved HFD-induced insulin resistance.

Conclusion: These results indicate that 25HC3S decreases lipogenesis by inhibiting the LXR\(\alpha\)/SREBP-1c signaling pathway and oxysterol sulfation can be a key protective regulatory pathway against lipid accumulation and lipid-induced inflammation in vivo.

Biography
Shunlin Ren, Research Career Scientist and Associate Professor, received his Ph.D. degree from Virginia Commonwealth University. His research is supported by NIH R01, VA Merit Review grants, and Research Career Scientist Award. He is a principal investigator. He has published more than 50 papers in reputed journals and serving as an editorial board member of repute.

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