**Hepatic selenoprotein S knockout aggravates diet-induced MAFLD through modulating LPC-autotaxin-LPA axis**

**Aim**

Hepatic selenoprotein S (SelS) knockout (*SelSH-KO*) exacerbates high-fat diet (HFD)-induced insulin resistance (IR), glucolipid metabolic disorders and hepatic steatosis. This study aims to characterized changes of lipid metabolites in the livers of *SelSH-KO* mice by untargeted lipidomic analysis in order to achieving a better understanding metabolic pathways involved in MAFLD.

**Method**

After 4 weeks of adaptive feeding, male *SelSH-KO* and control *SelSF/F* mice were fed either a HFD or regular chow (RC) for an additional 20 weeks. Liver tissues were then collected for untargeted lipidomics analysis to profile differential lipid metabolites. Quantitative measurements of hepatic lysophosphatidylcholine (LPC) levels, as well as serum LPC, autotaxin (ATX), lysophosphatidic acid (LPA), fibroblast growth factor 21 (FGF21) and adiponectin were performed using enzyme-linked immunosorbent assay (ELISA) kits. RT-qPCR was employed to detect LPA receptors mRNA expression. Western blotting was conducted to examine the protein levels of ATX and the phosphorylation of Erk and PPARα.

**Results**

Untargeted lipidomics analysis revealed 160 hepatic lipid metabolites showed significant differences between the two genotypes under HFD feeding conditions, characterized primarily by upregulated triglycerides and downregulated LPCs in *SelSH-KO*mice compared to *SelSF/F* mice. Serum LPC concentrations were elevated in *SelSH-KO*mice, while hepatic LPC levels were reduced in S*elSH-KO* mice under HFD feeding conditions.

Both hepatic ATX mRNA expression and protein levels, as well as serum ATX levels were increased in *SelSH-KO*mice, which facilitated the conversion of LPC into LPA. As expected, serum LPA levels and LPA-binding G protein-coupled receptor expression were increased in *SelSH-KO*mice, leading to extracellular regulated protein kinase (Erk) activation and peroxisome proliferator-activated receptor α (PPARα) inhibition, subsequently disrupted the FGF21-adiponectin axis, thereby contributing to the progression of MAFLD.

**Conclusion**

Hepatic SelS knockout may exacerbate diet-induced MAFLD through the modulation of LPC-ATX-LPA axis, then mediating FGF21-adiponectin axis to maintain glycolipid metabolic homeostasis.