**Involvement of hepatokine α1-acid glycoprotein in the progression of MASLD**

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**Background and aims.**

Metabolic dysfunction-associated steatotic liver disease (MASLD) has an estimated global prevalence of 30%, and its prevalence has been revealed to be as high as 70% among obese individuals. Currently, there is a need to develop new therapeutic drugs based on the mechanism of MASLD progression. α1-acid glycoprotein (AGP) is one of the hepatokines produced in the liver. The presence of single nucleotide polymorphisms associated with MASLD and fluctuations in plasma levels have been reported for AGP, while its physiological function remains largely unclear. The study aimed to elucidate the involvement of AGP in the progression of MASLD.

**Methods.**

Endogenous AGP levels in MASLD were evaluated through reanalysis of a public liver RNA-Seq dataset from patients with fatty liver disease and analysis of high-fat diet (HFD)-induced MASLD mice. C57BL/6N (WT) and AGP-knockout (KO) mice were fed a normal diet (ND) or HFD for 12 weeks, and various evaluations were performed on the liver, adipose tissue, and plasma.

**Results.**

Reanalysis of the liver RNA-Seq dataset revealed that the expression levels of *ORM1* and *ORM2*, which encode human AGP, were significantly decreased as disease severity in patients with fatty liver disease. Similarly, in MASLD mice, hepatic and plasma levels of AGP were shown to decrease with disease progression. Following HFD feeding, AGP-KO mice exhibited further exacerbation of fatty liver, obesity, macrophage infiltration into adipose tissue, and impaired glucose tolerance compared to WT mice. In the liver of AGP-KO mice, the expression level of the mitochondrial biogenesis factor PGC-1α and the phosphorylation level of AMP-activated protein kinase were significantly reduced, suggesting a decrease in fatty acid β-oxidation.

**Conclusion/Discussion.**

This study suggested that reduced endogenous AGP levels in MASLD may contribute to disease progression by exacerbating adipose tissue inflammation and impairing hepatic glucose and lipid metabolism.