Abstract of thesis entitled

**Autotaxin as a New Mediator for** **Non-alcoholic Fatty Liver Disease:** **Mechanism and Therapeutic Interventions**

Submitted by

**QIU Han**

for the degree of Doctor of Philosophy

at the University of Hong Kong

in August 2021

Non-alcoholic fatty liver disease (NAFLD) refers to a spectrum of conditions caused by excessive accumulation of fat in the liver. NAFLD has emerged as the leading cause of chronic liver disease, and it is a major indication for liver transplantation globally. Therefore, the identification of new therapeutic targets for the development of clinical interventions for NAFLD is of great importance.

Autotaxin, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), is a secreted glycoprotein originally discovered in melanoma cells. Autotaxin is an enzyme responsible for producing lysophosphatidic acid (LPA)which binds with LPA receptors and exerts various pathophysiological effects. Previous studies have reported that serum autotaxin levels increase in NAFLD, but the exact metabolic role of autotaxin in NAFLD is unclear. Therefore, the aim of this study is to investigate 1) whether autotaxin plays a pathological role in the development of NAFLD, as well as 2) the mechanism underlying the action of autotaxin.

In this study, a novel role of autotaxin as a mediator to exacerbate NAFLD was discovered for the first time. Our clinical and animal studies demonstrated that liver-derived circulating autotaxin is positively associated with NAFLD. Knockdown of hepatic autotaxin markedly attenuated liver steatosis in mice subjected to high-fat diet (HFD), accompanied by significantly elevated hepatic fatty acid oxidation (FAO) rate. Moreover, anti-autotaxin neutralizing antibody mediated inhibition of circulating autotaxin activity significantly alleviated HFD-induced fatty liver. Notably, the expression levels of fibroblast growth factor 21 (FGF21), a well-known beneficial regulator in NAFLD, was also markedly increased after the inhibition of autotaxin activity. These results demonstrated autotaxin is a new mediator and a potential therapeutic target for NAFLD.

The beneficial effects of anti-autotaxin neutralizing antibody on NAFLD disappeared in mice with global FGF21 deficiency, indicating that the detrimental effect of autotaxin on NAFLD is mediated through altering FGF21 levels. Mechanistically, autotaxin inhibits FGF21 expression via LPA-Erk pathway induced phosphorylation of peroxisome proliferator-activated receptor alpha (PPARα) on its site of Serine (Ser) 21. Anti-autotaxin neutralizing antibody treatment blocks serum autotaxin activity, alleviates the inhibitory effect of autotaxin-LPA axis on FGF21 and promotes hepatic FGF21 expression. FGF21 further exerts direct or indirect beneficial metabolic effects on liver and alleviates the progression of NAFLD.

Collectively, our data suggest that liver-derived circulating autotaxin is closely associated with NAFLD, and autotaxin-LPA axis exacerbates NAFLD through inhibition of hepatic PPARα-regulated FGF21 expression. Thus, autotaxin mediates the development of NAFLD and it is a potential therapeutic target for the treatment of NAFLD.

(403 words)