Lysosomal Disturbances in Metabolic Disorders

Summary

Chapter 1 provides a global overview of MASLD, MASH, MetALD, ALD, and NPC1. First of all, the prevalence of the respective disorders as well as their mode of diagnosis and treatment are extensively introduced. Next, an overview of the function of the lysosome and lysosomal enzymes is given. Furthermore, lysosomes and lysosomal enzymes in the context of metabolic disorders are introduced in more detail. Finally, the aim of this thesis and the outline are summarized.

Chapter 2 investigates the role of plasma CTSD levels in the early stages of MetALD/ALD. The findings demonstrate that plasma CTSD levels are significantly higher in the very early stages of MetALD/ALD and outperformed the currently available non-invasive methods to detect MetALD/ALD. Those observations suggest that plasma CTSD levels could be a novel, non-invasive marker for detection of MetALD/ALD.

Chapter 3 explores whether plasma CTSD levels are associated with late stages of ALD. The data demonstrate that opposed to early-stage ALD, plasma CTSD levels reduced with increasing liver cirrhosis severity. Besides, plasma CTSD levels are inversely associated with liver disease severity independent of alcohol intake. This suggests that liver disease severity has a significant impact on plasma CTSD levels.

Chapter 4 investigates CTSD as a therapeutic target for the treatment of MASH. The impact of inhibition of intra-and extracellular CTSD on the liver lipidome was detected in *Ldlr*$^{-/-}$ MASH mice using MALDI-MSI technique. We observed that intracellular CTSD inhibition regulated the specific lipid composition that is linked to mitochondrial dysfunction and inflammation and induced more oxidative stress compared to extracellular CTSD inhibition. The observed modifications in lipid composition demonstrate that extracellular CTSD inhibition is a potentially beneficial therapeutic approach for MASH.

Chapter 5 demonstrates another lysosomal enzyme acid phosphatase (AP) activity is associated with MetS in obese adolescents and adults. We observed that plasma AP activity has a strong positive association with triglycerides in obese subjects. Our data suggests that plasma AP activity has the potential to be used as a robust parameter to assist with detecting MetS in both adolescents and adults.

Chapter 6 investigates the cause and the potential mechanisms for splenomegaly in NPC1 disease. In this chapter, the data demonstrates that NPC1 null mutation leads to increased plasma levels of G-CSF and HSCs from bone marrow to spleen, which may contribute to spleen enlargement in patients with NPC1 disease.

Chapter 7 gives an overview of the role of cathepsins in MASH and MASH-HCC and argues the crucial role of cathepsins in mediating the transition from MASH to HCC. After introducing the current epidemiological prevalence, mechanisms of cathepsins and an overview of pathophysiological hepatic processes in MASH and MASH-HCC are interpreted. Finally, the therapeutic potential of cathepsins and their related clinical implications in NASH-HCC are discussed.

Chapter 8 discusses the major findings and overall conclusion of this thesis in the context of all indicated metabolic disorders, offering a perspective on the research field and underscoring the clinical implications of the results.