The lysosomal enzyme cathepsin D as novel therapeutic target for non-alcoholic steatohepatitis

The decrease in physical activity combined with increased caloric intake has led us to a global obesity epidemic. Obese patients can develop metabolic syndrome (MetS), which is a term used to assess the risk of a patient to develop several obesity-related disorders. One such disorder is related to the disturbances of liver and is referred to as non-alcoholic fatty liver disease (NAFLD), a condition where lipids uncontrollably accumulate inside liver cells.

NAFLD covers a disease spectrum of several stages ranging from a liver that only accumulates lipids (then referred to as a fatty liver) to a liver that stores lipids in combination with the representation of inflammatory infiltrates and scarring tissue (= fibrosis), which is then called non-alcoholic steatohepatitis (NASH). NASH is a disease stage that can further progress into more advanced liver diseases such as liver cirrhosis and hepatocellular carcinoma. It is therefore of importance to prevent the development of those advanced liver diseases and tackle the inflammatory response in the liver as soon as possible. However, a major issue in the development of effective therapeutic approaches for NASH is the lack of knowledge in the mechanisms driving the inflammatory reaction in the liver.

Previous research in our group identified a key role for lysosomes, which are intracellular organelles, in hepatic macrophages in regulating the inflammatory reaction during NASH. In the healthy state, lysosomes of macrophages ensure that intracellular lipids are converted into smaller building blocks that can be transported throughout and eventually out of the cell. Under NASH conditions, however, lysosomes cannot degrade the lipids as efficiently into smaller building blocks, leading to the accumulation of lipids in the lysosomes of the macrophages, leading to lysosomal dysfunction. Due to disturbances in lysosomal physiology, we observed aberrant excretion of lysosomal enzymes in the plasma. Indeed, we demonstrated that plasma levels of the lysosomal enzyme cathepsin D could distinguish between patients with and without inflammation in the liver, thereby providing solid evidence for the role of lysosomes in NASH.

As a follow-up question, we questioned whether cathepsin D itself also contributes to the development of hepatic inflammation.

To answer this question, we made use of a mouse model that represents early stages of NASH. Next, by injecting these mice with a compound that blocks cathepsin D in the final week or during the whole course of the experiment, we investigated whether cathepsin D contributes to the inflammatory response in the liver. Our results demonstrated that blocking the function of cathepsin D resulted in reduced inflammation. Moreover, we also observed an impressive improvement in lipid metabolism, with increased fecal excretion of cholesterol and reduced systemic lipid levels.

These results indicate that besides its potential as a diagnostic marker for NASH, cathepsin D is

also contributing to hepatic inflammation and can therefore be considered as a new therapeutic target.

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Cathepsin D regulates lipid metabolism in murine steatohepatitis.
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