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Title of project: Impaired hepatic NAD+ metabolism as a novel driver of liver fibrosis

ABSTRACT

Global prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing. NAFLD can progress to nonalcoholic steatohepatitis (NASH), characterized by steatosis, fibrosis, inflammation, and hepatocyte cell death. As this condition can be fatal for patients, there is an urgent need to identify treatment targets for the components of NASH. We have previously observed that mice with impaired hepatic synthesis of nicotinamide adenine dinucleotide (NAD+) are more susceptible towards fibrosis development. Furthermore, we find that hepatic inflammation can be attenuated by supplementation with the NAD+ precursor nicotinamide riboside (NR). As chronic liver inflammation leads to fibrosis, NR supplementation provides a potential treatment strategy for liver fibrosis. However, it is currently not known how impaired NAD+ synthesis confers increased susceptibility towards fibrosis and how NR attenuates inflammation. We hypothesize that decreased hepatic NAD+ content confers increased susceptibility towards NASH, and that liver fibrosis and inflammation can be resolved through NR supplementation. The over-arching goal of the project is to understand how impaired NAD+ biosynthesis confers increased susceptibility to liver fibrosis development. In this project, we will identify the hepatic pathways in the liver induced by NR, and define the cell types responsible for fibrosis progression to identify the link behind NAD+ metabolism and fibrosis development. Studies will be carried out in hepatocyte-specific Nampt knockout (HNKO) mice, which is a mouse strain with impaired ability to synthesize NAD+ from nicotinamide in the liver. This mouse strain has a plasma biomarker profile resembling human NAFLD, and is therefore an interesting model for investigating fibrosis progression. The project will identify how the liver proteome is affected by dietary NR supplementation, which will identify the specific pathways induced through the treatment. Furthermore, we will determine how specific cell populations are affected by NR through single-nucleus RNA sequencing and single molecule fluorescence in situ hybridization to get a thorough picture of how the various cells in the liver are affected by NR. The project will also address basic scientific questions about liver zonation to determine potential zone-specific differences in NAD+ metabolism in the liver. This may provide novel insights into the therapeutic potential of NR for resolving liver fibrosis. Data from this project will explore the mechanisms behind a promising treatment strategy for resolving liver fibrosis and inflammation, with a putative translational potential.