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Molecular Pathogenesis of NASH through the Dysregulation of Metabolic Organ Network in the NASH-HCC Model Mouse Treated with Streptozotocin-High Fat Diet

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Abstract : NASH is an increasingly prevalent chronic liver disease that can progress to hepatocellular carcinoma and now is attracting interest worldwide. The STAM™ model is a clinically-correlated murine NASH model which shows the same pathological progression as NASH patients and has been widely used for pharmacological and basic research. The multiple parallel hits hypothesis suggests abnormalities in adipocytokines, intestinal microflora, and endotoxins are intertwined and could contribute to the development of NASH. In fact, NASH patients often exhibit gut dysbiosis and dysfunction in adipose tissue and metabolism. However, the analysis of the STAM™ model has only focused on the liver. To clarify whether the STAM™ model can also mimic multiple pathways of NASH progression, we analyzed the organ crosstalk interactions between the liver and the gut and the phenotype of adipose tissue in the STAM™ model. NASH was induced in male mice by a single subcutaneous injection of 200 µg streptozotocin 2 days after birth and feeding with high-fat diet after 4 weeks of age. The mice were sacrificed at NASH stage. Colon samples were snap-frozen in liquid nitrogen and stored at -80˚C for tight junction-related protein analysis. Adipose tissue was prepared into paraffin blocks for HE staining. Blood adiponectin was analyzed to confirm changes in the adipocytokine profile. Tight junction-related proteins in the intestine showed that expression of ZO-1 decreased with the progression of the disease. Increased expression of endotoxin in the blood and decreased expression of Adiponectin were also observed. HE staining revealed hypertrophy of adipocytes. Decreased expression of ZO-1 in the intestine of STAM™ mice suggests the occurrence of leaky gut, and abnormalities in adipocytokine secretion were also observed. Together with the liver, phenotypes in these organs are highly similar to human NASH patients and might be involved in the pathogenesis of NASH.

Keywords : Non-alcoholic steatohepatitis, hepatocellular carcinoma, fibrosis, organ crosstalk, leaky gut
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