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RNA-seq Analysis of Liver from NASH-HCC Model Mouse Treated with Streptozotocin-High Fat Diet

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Abstract : Non-alcoholic steatohepatitis (NASH) is a chronic liver disease, often associated with type II diabetes, which sometimes progresses to more serious conditions such as liver fibrosis and hepatocellular carcinoma (HCC). NASH has become an important health problem worldwide, buttherapeutic agents for NASH have not yet been approved, and animal models with high clinical correlation are required. TheSTAM™ mouse shows the same pathological progression as human NASH patients and has been widely used for both drug efficacy and basic research, such as lipid profiling and gut microbiota research. In this study, we analyzed the RNA-seq data of STAM™mice at each pathological stage (steatosis, steatohepatitis, liver fibrosis, and HCC) and examined the clinical correlation at the genetic level. NASH was induced in male mice by a single subcutaneous injection of 200 µg streptozotocin solution 2 days after birth and feeding with high fat dietafter 4 weeks of age. The mice were sacrificed and livers collected at 6, 8, 10, 12, 16, and 20 weeks of age. For liver samples, the left lateral lobe was snap frozen in liquid nitrogen and stored at -80˚C for RNA-seq analysis. Total RNA of the cells was isolated using RNeasy mini kit. The gene expression of the canonical pathways in NASH progression from steatosis to hepatocellular carcinoma were analyzed, such as immune system process, oxidation-reduction process, lipid metabolic process. Moreover, since it has been reported that genetic traits are involved in the development of NASH-HCC, we next analyzed the genetic mutations in the STAM™mice. The number of individuals showing mutations in Mtorinvolved in Insulin signaling increases as the disease progresses, especially in the liver cancer phase. These results indicated a clinical correlation of gene profiles in the STAM™mouse.

Keywords : steatosis, non-alcoholic steatohepatitis, fibrosis, hepatocellular carcinoma, RNA-seq
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