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2. Title

Effects of Nicotine on the Onset, Progression and Carcinogenesis in Nonalcoholic Steatohepatitis.

3. Period

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4. Summary

[Background] Non-alcoholic fatty liver disease (NAFLD) has been increasing worldwide and becoming the most frequent cause of liver disease. Non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD characterized by sustained inflammation and fibrosis, eventually developing liver cirrhosis and hepatocellular carcinoma. It is well established that nicotine has no small anti-inflammatory effect, while little is known about the suppressive role of nicotine in the pathogenesis and progression of NASH. Here we focused on the inhibitory effect of nicotine in the development of NASH using melanocortin 4 receptor-deficient (MC4R-KO) mice, novel NASH model mice.

[Methods] After 16-week western diet feeding, MC4R-KO mice were perfused with PBS and collagenase from the portal vein, and the liver was dispersed using gentle MACS dissociator. Hepatic non-parenchymal cells were collected by density gradient centrifugation and used for NX1-seq. single-cell transcriptome analysis.

Nicotine (0.3 mg/kg body weight) was injected intraperitoneally, twice a week, to male MC4R null mice from eight-weeks old for 16 weeks. Blood and tissue samples were collected from the mice to examine liver steatosis, inflammatory response, and liver fibrosis.

[Results] In single-cell analysis, gene expression changes were observed in hepatic macrophages from MC4R deficient mice with a high-fat diet, compared with wild-type mice with a high-fat diet or MC4R deficient mice with a control diet. The new cell cluster expressed SPP1 and showed a signature profile of gene expression. A part of the SPP1-positive macrophages were localized in hepatic crown-like structure and infiltrated closely to activated hepatic stellate cells.

Nicotine administration to MC4R null mice significantly reduced body weight, liver weight, and liver damage. Pericellular fibrosis in the liver were suppressed in the mice treated with nicotine, and the expression of genes related to lipogenesis, inflammation, and fibrosis were significantly inhibited by nicotine treatment.

[Conclusions] Inflammatory cells, including macrophages infiltrated in hepatic tissue, could drastically make a qualitative and quantitative transformation with the NASH development. SPP1-positive macrophages, which dominantly infiltrated in NASH liver, could be involved in the pathogenesis of NASH.

Nicotine might have an inhibitory effect on the NASH development by suppressing liver fibrosis..