

Establishment of the method of three-dimensional organoid culture derived from liver tissues of non-alcoholic steatohepatitis (NASH) model mice

Yamanaka Megumi¹, Elbadawy Mohamed¹, Kimika Hayasi¹, Yuta Goto¹, Ryouichi Tsunedomi², Shoichi Hazama^{2,3}, Hiroaki Nagano², Toshinori Yoshida⁴, Makoto Shibutani⁴, Ryo Ichikawa⁴, Junta Nakahara⁴, Tsutomu Omatsu⁵, Tetsuya Mizutani⁵, Yukie Katayama⁵, Yuta Shinohara^{1,6}, Masahiro Kaneda⁷, Hideyuki Yamawaki⁸, Tatsuya Usui¹, Kazuaki Sasaki¹

¹Lab. Vet Pharm., Dept Vet Med., Tokyo Agri&Tech Univ., ²Dept. Gastro-Breast & Endocrine Surgery, Grad. Sch. Med, Yamaguchi Univ., ³Dept. Translational Res. & Develop. Therap. against Cancer., Sch. Med, Yamaguchi Univ., ⁴Lab. Vet Pathol., Dept Vet. Med., Tokyo Agri&Tech Univ., ⁵Res & Edu Ctr., Dept Vet Med., Tokyo Agri&Tech Univ., ⁶Pet Health & Food Division, Iuskura Industry, ⁷Lab. Vet Anatomy., Dept Vet Med., Tokyo Agri&Tech Univ., ⁸Lab. Vet Pharm., Dept Vet Med., Kitasato Univ.

【Background】

Nowadays, there are many non-alcoholic steatohepatitis (NASH) patients who develop fatty liver without alcohol. NASH patients usually progress to liver cirrhosis or liver cancer in the future. However, the detailed pathogenic mechanisms still have not been clarified. Therefore, a new approach is required to establish the therapeutic method of NASH disease.

【Object】

To clarify the usefulness of organoids derived from liver tissue of NASH model mice, we examined the correlation between the histopathology of disease progression of NASH mice and the function and histology of liver organoids.

【Methods】

Seven-week-old C57BL / 6J mice were fed a diet for 4, 8, and 12 weeks to induce different stages of NASH disease. After measuring liver weight and blood parameters of NASH mice, the histopathological structure of liver tissue was analyzed. Using isolated the liver tissues, we generated liver organoids and checked the histopathology and functions of them.

【Result and discussion】

Liver organoid formation and expression of hepatocyte markers, albumin, AFP and CYP3A4 / 5 were observed in all groups of NASH mice. Liver organoids from mice fed a NASH diet for 4 weeks showed the highest organoid-forming ability. And liver organoids from mice fed a NASH diet for 12 weeks showed epithelial-mesenchymal transition with a decrease in intercellular adhesion and an increase in collagen I expression. These results suggest that liver organoids derived from NASH model mice may recapitulate the characteristics of liver fibrosis and become a new research tool for NASH disease.