Establishment of orthotopic transplantation model of mouse gallbladder cancer organoid for development and efficacy evaluation of anti-tumor agents.

Kato Shingo[1], Tetsuya Matsuura[2], Daisuke Kurotaki[3], Yoshitaka Hippo[4], Tomohiko Tamura[3], Atsushi Nakajima[2]

[1]Dept. Clinical Cancer Genomics, Yokohama City University Hospital, [2]Dept. Gastroenterology and Hepatology, Grad. Sch. Med., Yokohama Univ., [3]Dept. Immunology., Grad. Sch. Med., Yokohama Univ., [4]Division of Molecular Carcinogenesis, Chiba Cancer Center Research Institute

Gallbladder cancer (GBC) is relatively rare worldwide. For such rare cancer, the development of animal models is more important because it is difficult to develop optimal treatments in large-scale clinical trials. Additionally, considering that immunotherapy has emerged as a promising new modality of treatment for biliary tract cancers, to develop animal models that can analyze host immune response against cancer is becoming more important. Based on these backgrounds, we aimed to establish an orthotopic GBC mouse model. To reflect genetic alterations observed in human GBC, we first developed mouse gallbladder organoids with genetic alterations in the Kras and Trp53 genes. The knockout of Trp53 gene was introduced by CRISPR-Cas9 system. These GBC organoids could create a subcutaneous tumor in wild type mice with normal anti-tumor immunity. Additionally, an orthotopic transplant model was successfully established in wild type mice. The populations of the subsets of tumor-infiltrating immune cells were able to be analyzed in both the subcutaneous tumor model and the orthotopic transplant model. In both models, the percentage of $CD8^+$ T cells was slightly decreased and that of $CD11b^+$ $Ly6G^+$ cells significantly increased with tumor growth. Finally, the treatment of orthotopic transplant model by gemcitabine significantly decreased tumor volumes. In conclusion, we developed a novel GBC mouse model by which we can analyze tumor immune response and the efficacy of anti-tumor agents.