1. No.

   2021G001

2. Title

   Analysis of immunological microenvironment of tumor and effect of smoking habits for the development of personalized medicine in liver cancer

3. Period

   2021-2023

4. Summary

   The aim of this study was to analyze the clinical background and genomic and epigenomic alteratins associated with tumor immune microenvironment (TIME) in hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCA) to obtain basic data for biomarker development in ICI therapy.

   First, we investigated the association of TIME with cancer-related gene mutations in HCC cases, which were classified based on mRNA expression and immunohistochemistry. In addition, we analyzed the association between TIME and efficacy of PD-1 antibody treatment using biopsy tissue from 34 HCC patients who had received PD-1 antibody prior to ICI treatment. HCCs with active mutations in the PI3K-Akt pathway were more common in the inflamed type, and HCC with active mutations in the β-catenin pathway were more common in the non-inflamed type. TIME of tumor could stratify progression-free survival after anti-PD-1 antibody therapy.

   Next, we analyzed the characteristics of anti-PD-1 antibody-resistant tumors by comparing TIME, genomic aberrations, and antitumor response using tumor tissue and plasma from patients who received adjuvant anti-PD-1 antibody after locoregional therapy for HCC. The results suggest that patients with inflamed type TIME are more likely to respond to adjuvant therapy with ICI.

   Finally, we analyzed the characteristics associated with non-inflamed type CCA using data on cancer-associated gene mutations, mRNA expression, and DNA methylation in 36 CCA cases. Non-inflamed CCA was associated with decreased expression/gene methylation of antigen presentation machineries and IDH1/2 gene mutations. It is known that IDH1/2 mutations induce epigenomic abnormalities; it could be possible that IDH1/2 mutations may be involved in the formation of non-inflamed CCA.