Prediction of therapeutic effect of combined immunotherapy using tumor microenvironment analysis and MRI images of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is known as a cancer with a high recurrence rate and poor prognosis. Pharmacotherapy such as anti-PD-L1 antibody/anti-VEGF antibody combination immunotherapy (atezolizumab/bevacizumab) becomes applicable to advanced HCC, but its efficacy is limited. Therefore, there is a need for biomarkers that can predict the therapeutic efficacy of each drug. In this study, we performed a multi-omics analysis using resected specimens from over 100 HCC patients and found that steatotic HCC, which is characterized by fat droplet accumulation within cancer cells, is in a state of immune exhaustion that is more likely to benefit from immune checkpoint inhibitors. We showed that steatotic HCC patients identified by MRI images have a better response to combination immunotherapy.

Background & Results

According to WHO statistics, liver cancer is the third most common cancer in terms of deaths (approximately 830,000). In Japan, the annual number of deaths reaches 25,000, and the five-year survival rate is reported to be 35.8%. In recent years, a variety of drugs have been developed to treat advanced cases, and a total of eight treatment options exist, centered on the first-line anti-PD-L1 antibody/anti-VEGF antibody combination immunotherapy (atezolizumab/bevacizumab). On the other hand, the problem is that less than 30% of patients achieve tumor disappearance/reduction with any of these therapies. Therefore, "personalized medicine," in which the most appropriate drug is selected for each patient, is important to improve prognosis, and the development of biomarkers to predict therapeutic efficacy of each drug is an urgent issue. We performed transcriptomic and genomic analyses using resected HCC tissues from 113 patients. We analyzed the tumor immune microenvironment and examined the relationship with clinicopathological factors. As a result, we found that steatotic HCC, in which cancer cells have fat droplet accumulation, shows strong immune cell infiltration in the tumor, while the infiltrated immune cells are exhausted. Lipidomic analysis identified that palmitic acid, a type of saturated fatty acid, increased in steatotic HCC. Furthermore, we found that palmitic acid increases the expression of PD-L1 on the membrane surface of HCC cells. Finally, we have shown that steatotic HCC can be identified by MRI imaging and are highly sensitive to atezolizumab-bevacizumab combination therapy.

Significance of the research and Future perspective

By predicting the therapeutic effect of combined immunotherapy in advance, it is expected to contribute to improving the prognosis of patients with advanced HCC by enabling more optimal drug selection among various drug therapy options. In addition, since MRI is performed for the diagnosis of HCC, it is expected to be a patient-friendly noninvasive biomarker. Furthermore, this study is expected to lead to the development of therapeutic agents targeting the immune escape mechanism of HCC via fat droplet accumulation.

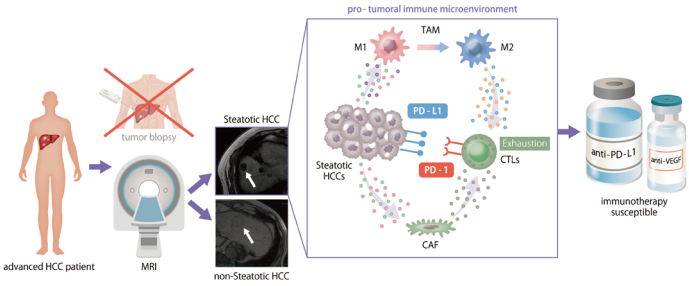

Figure 1

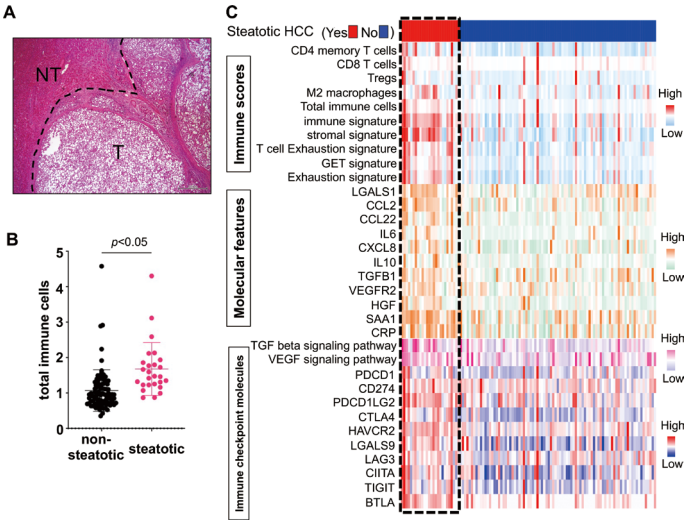

Figure 2

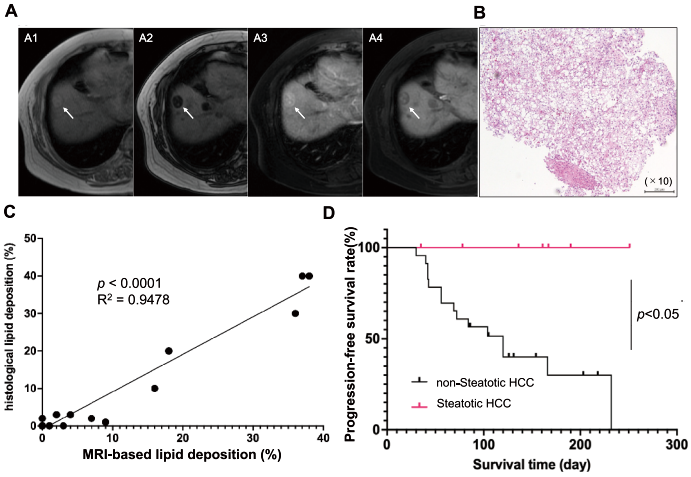

Figure 3

Patent PCT/JP2023/016673

Treatise Murai, Hiroki; Kodama, Takahiro; Maesaka, Kazuki et al. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. Hepatology 2023, 77(1), 77-91. doi: 10.1002/hep.32573

URL

Keyword steatotic HCC, immune exhaustion, immune checkpoint inhibitor, MRI, biomarker