論　文　内　容　要　旨

The presence of vessels encapsulating tumor clusters is associated with an immunosuppressive tumor microenvironment in hepatocellular carcinoma

（肝細胞癌周囲の類洞様血管構造（vessels that encapsulated tumor clusters; VETC）の腫瘍免疫抑制環境との関連）

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The treatment strategy for hepatocellular carcinoma (HCC) depends on the disease stage and underlying conditions. Unresectable HCC presents a very limited range of treatments; therefore, any potential stratification of patients could facilitate development of the most effective treatment option. Recently, a distinct vascular pattern in HCC called vessels encapsulating tumor-forming clusters (VETC) has received attention because of its association with poor prognosis. However, little is known about the mechanism by which VETC promotes an aggressive phenotype at the molecular level.

In this single-center retrospective study, the association between differences in stepwise signal intensity in the HB phase and molecular subtypes and somatic mutations associated with the immune microenvironment were investigated using the International Cancer Genome Consortium (ICGC) cohort (66 patients).

Although there was no difference in recurrence free survival, the VETC+ HCC group showed significantly lower overall survival (OS) and higher cumulative incidence of extrahepatic metastasis after curative hepatic resection than the VETC- HCC group. The VETC+ group exhibited molecular features indicative of lower immune activation than the VETC- group, suggesting that tumor cells in the VETC+ group were more likely to escape from the immune response, which could lead to the shorter OS and higher risk of metastasis.

On the other hand, gene expression levels of fibroblast growth factor receptors were upregulated in VETC+ HCC, combination with our report that tumor FGFR4 level can predict the efficacy of lenvatinib treatment in patients with advanced HCC, suggesting that VETC+ HCC might benefit from lenvatinib treatment.

Additionally, VETC+HCC has significantly fewer mutations associated with chromatin remodeling, which might imply a weak association of VETC+HCC with DNA modification. The characteristics of the mutation profile of VETC+ is different from VETC-, implying that VETC is derived via carcinogenesis rather than originating from non-VETC tissue.

To our knowledge, this is the first study to analyze the molecular patterns of VETC using RNA-Seq data. Our results revealed that the molecular characteristics of VETC are associated with suppression of the tumor immune system. Although further study is necessary, these findings highlight the importance of assessing VETC status for more effective treatment of HCC.